EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2019
EMA/547408/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Benlysta

International non-proprietary name: belimumab

Procedure No. EMEA/H/C/002015/II/0062

Note

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

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List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ANA	Anti-nuclear antibody
Anti-dsDNA	Anti-double stranded deoxyribonucleic acid
BILAG	British Isles Lupus Assessment Group
CI	Confidence interval
Cmax	Maximum concentration
Cmin	Minimum concentration
CNS	Central nervous system
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DAIs	Disease Activity Indices
DB	Double-blind
dL	Deciliter
DLP	Data lock point
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DO=NR	Dropout = Non-Responder
DO/TF = NR	Drop Out/Treatment Failure = Non-Responder
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GC	Generic core
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
ITT	Intention-to-Treat
IV	Intravenous(ly)
IVIG	Intravenous immunoglobulin
kg	Kilogram
LLN	Lower limit of normal lower
LOCF	Last observation carried forward
LOQ	Limit of quantification
NSAID	Non-steroidal anti-inflammatory drug
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MITT	Modified Intention-to-Treat
mL	Milliliter
MMF	Mycophenolate mofetil

NMSC	Non-melanoma skin cancer
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
ParentGA	Parent's Global Assessment
PC	Placebo-controlled
PCS	Physical component summary
PIP	Paediatric Investigation Plan
PedsQL	Paediatric Quality of Life Inventory – Generic Core Scale
PedsQL-Fatigue	Paediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale
PG	Parallel Group
PGA	Physician's Global Assessment
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PRCSG	Paediatric Rheumatology Collaborative Study Group
PREA	Paediatric Research Equity Act
PRINTO	Paediatric Rheumatology International Trials Organization
PRO	Patient-reported Outcomes
PSP	Paediatric Study Plan
QoL	Quality of life
R	Randomized
RAP	Reporting and Analysis Plan
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index	
SE	Standard error
SELENA	Safety of Estrogen in Lupus Erythematosus National Assessment
SF-36	Short Form 36-item health survey
SFI	Systemic lupus erythematosus (SLE) Flare Index
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SRI	SLE Responder Index
TNF	Tumor necrosis factor
US	United States
ULN	Upper limit of normal
VAS	Visual analog scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline (Ireland) Limited submitted to the European Medicines Agency on 9 November 2018 an application for a variation.

The following variation was requested:

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

Extension of indication to include patients aged 5 years and older in the current approved indication for Benlysta (belimumab powder for solution for infusion 120 mg/ml and 400 mg/ml) based on the results of the safety, efficacy and pharmacokinetics study in patients aged 5 years to 17 years (BEL114055). As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated with safety and efficacy information.
Update of sections 4.2, 5.1 and 5.2 of the SmPC for Benlysta (belimumab, solution for injection in pre-filled pen and pre-filled syringe, 200 mg) to reflect the paediatric data available for the intravenous formulation. The Package Leaflet is updated accordingly.
The RMP version 28.0 is submitted to reflect the results of the study and to bring it in line with the GVP Module V RMP template version 2.0. In addition, the MAH took the opportunity to make some editorial changes in the product information and bring it in line with the latest QRD template version 10.0.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2016, the application included an EMA Decision P/0183/2006 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0183/2016 was completed.

The PDCO issued an opinion on compliance for the PIP EMEA-C-000520-PIP01-08-M05.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	9 November 2018
Start of procedure:	1 December 2018
CHMP Rapporteur Assessment Report	25 January 2019
PRAC Rapporteur Assessment Report	25 January 2019
PRAC Outcome	14 February 2019
CHMP members comments	20 February 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 February 2019
Request for supplementary information (RSI)	28 February 2019
CHMP Rapporteur Assessment Report	27 May 2019
PRAC Rapporteur Assessment Report	27 May 2019
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	14 June 2019
CHMP members comments	18 June 2019
Updated CHMP Rapporteur Assessment Report	20 June 2019
2nd Request for supplementary information (RSI)	27 June 2019
Submission date of MAH responses	16 August 2019
Re-start of procedure	21 August 2019
PRAC Rapporteur Assessment Report	26 August 2019
PRAC members comments	26 August 2019
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	n/a
PRAC Outcome	5 September 2019
CHMP members comments	5 September 2019
Updated CHMP Rapporteur Assessment Report	5 September 2019
Opinion	19 September 2019

2. Scientific discussion

2.1. Introduction

About the product

Belimumab is a human IgG1λ monoclonal antibody specific for soluble human lymphocyte stimulator protein licensed for treatment of systemic lupus erythematosus (SLE) in adult patients. Belimumab does not bind B cells directly, but by binding BLyS, belimumab inhibits the survival of B cells, including

autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin-producing plasma cells.

Belimumab was approved in EU in 2011 for IV use, and in 2017 for SC use. Belimumab intravenous is currently approved in the US, all European Economic Area countries, Japan as well as over 40 further countries. Belimumab subcutaneous injection is currently approved in the US, all European Economic Area countries, Japan and Canada. Benlysta is currently not approved for Paediatric use. The MAH proposed to extend the indication extension to include Paediatric patients based on a Benlysta IV study (BEL114055) in Paediatric patients:

"*Belimumab is indicated as add-on therapy in patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy*."

The basis for the application is a phase 2 study, agreed in the PIP at the approval of Benlysta. The study was not powered for any formal comparisons between Benlysta and placebo, and the efficacy and safety needs to be extrapolated to children using PK data and a numerical comparison of the clinical results between the Paediatric and adult studies.

The results of the study BEL114055 Part A were submitted on 17th July 2018 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The data were assessed as part of procedure EMEA/H/C/002015/P46/030 which concluded that "*The results from BEL144055 will be thoroughly assessed when the MAH submits a planned variation for an indication in paediatric patients*."

The proposed IV dose in Paediatric patients 5 to 17 years of age is the same as that approved in adults: 10 mg/kg belimumab administered as an IV infusion at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

SLE

SLE predominantly affects female patients between the ages of 15 and 40, and in approximately 10-20% of SLE patients, disease onset occurs prior to 20 years of age [Aggarwal, 2015; Kamphuis, 2010; Klein-Gitelman, 2002; Malattia, 2013]. Regardless of age of onset or time of diagnosis, SLE patients share many immunogenetic and serologic similarities [Aggarwal, 2015; Barron, 1993; Livingston, 2012; Mina, 2013]. It has been reported that there are some differences in clinical features in childhood-onset SLE [Aggarwal, 2015; Brunner 2008; Costallat, 1994; Mina, 2013; Tucker, 1995].

Prepubertal onset of SLE is uncommon, and more often associated to rare monogenic variants, for example mutations in the complement system. Paediatric SLE patients tend to have more active disease both at the time of diagnosis and over time [Kamphuis, 2010; Livingston, 2012; Mina, 2013]. In a study by Brunner et al, the mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score in Paediatric SLE patients at diagnosis was 1.7 times the score in adult SLE patients (16.8 vs. 9.3, respectively) [Brunner, 2008]. SLE in children can be associated with more rapid accrual of damage and may have a higher degree of morbidity compared with SLE in adult populations [Brunner, 2008; Kamphuis, 2010; Levy, 2012; Malattia, 2013; Tucker, 2008]. In a global study by the PRINTO, damage was present in 58.2% of the patients who had disease duration more than 5 years [Gutiérrez-Suárez, 2006]. The range of organ involvements in Paediatric SLE is generally similar to adult SLE with some manifestations more prevalent in children, such as renal lupus, malar rash, seizures, oral ulcers, hemolytic anemia, and thrombocytopenia [Aggarwal, 2015; Barron, 1993; Brunner, 2008; Fonseca, 2018; Mina, 2013; Webb, 2011]. Glomerulonephritis and neurologic involvement represent significant disease burden in SLE and occurred at higher frequency in Paediatric SLE [Amaral, 2014; Ambrose, 2016; Barron, 1993; Fish, 1977; Fonseca, 2018; King, 1977; Tarr, 2015; Tucker, 2008]. Growth failure and delayed puberty are complications of SLE specific to children that may have a serious psychological

impact. The frequency of both events increased significantly with the increase in disease duration [Gutiérrez-Suárez, 2006].

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

SLE incidence and prevalence increase with age during childhood, and diagnosis is uncommon in children aged ≤9 years [Hiraki, 2012; Lim, 2009; Nightingale, 2007; Somers, 2007]. In a US study of claims data, the incidence of SLE was 0.13, 1.92 and 6.40 per 100,000 per year in children aged 3 to <6, 9 to <12 and 15 to <18 years of age [Hiraki, 2012]. In a population based study in the United Kingdom, 0 and 1 incident case were identified in children aged <10, and 10-19 respectively [Hopkinson, 1993]. A limitation of these estimates is that they are based on small sample sizes and are therefore subject to some uncertainty.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

Being natural proteins, therapeutic antibodies such as benlysta, are not excreted unchanged and do not give rise to metabolites with potential biological activity. In view of this, guidance on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) especially exempt amino acids, peptides and proteins from the need for a complete environmental assessment and therefore, no assessment of the ERA for Benlysta is needed.

2.2.2. Conclusion on the non-clinical aspects

The non-clinical aspects are considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1. Description of Clinical Efficacy and Safety Studies

Protocol No. Location of Study Report (when applicable)	No. Study Centers Location(s)	Study Start; Enrollment Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender F/M; Mean Age (Range)	Primary Endpoint(s)
Randomized, Placebo-controlled Trial of Belimumab Administered IV in Pediatric Subjects with SLE									
BEL114055 m5	39 centers in 10 countries: Argentina, Canada, Japan, Mexico, Peru, Poland, Russian Federation, Spain, UK, and US	Sep 2012 52-week DB Phase (Part A) Completed: Jan 2018 Long-term OL for completers (Part B) and long-term follow-up for withdrawals (Part C) are ongoing. 93/at least 70	To evaluate the safety, efficacy, and PK of belimumab in pediatric subjects ages 5 years to 17 years of age with active systemic SLE	MC, R, DB, PC	Active autoantibody positive SLE, stable SLE treatment regimen	Placebo or Belimumab 10 mg/kg; IV infusion; 52 weeks (Part A)	Placebo: 40/31 Belimumab 10 mg/kg: 53/45	88F 5M 14Y (6-17Y)	SRI Response at Week 52 (≥4 point reduction from baseline in SS score and no worsening in PGA and no new BILAG 1A/2B)

Protocol No. Location of Study Report (when applicable)	No. Study Centers Location(s)	Study Start; Enrollment Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender F/M; Mean Age (Range)	Primary Endpoint(s)
Randomized, Placebo-controlled Trials of Belimumab Administered IV in Adult Subjects with SLE									
HGS1006-C1056/ BEL110751 m5	136 centers in 19 countries across 3 regions: North America, Europe, and Latin America	Feb 2007 Completed: Mar 2010 819/810	To evaluate the efficacy, safety, tolerability, and impact on quality of life of IV belimumab in subjects with SLE	MC, R, DB, PC	Active SLE disease defined as SS disease activity score ≥6, stable SLE treatment regimen, positive ANA/ anti-dsDNA	Placebo or Belimumab 1 or 10 mg/kg on Days 0, 14, 28, and every 28 days thereafter; IV infusion; 76 weeks	Placebo: 275/205 IV Belimumab 1 mg/kg: 271/216 10 mg/kg: 273/209	764F 55M 40.2Y (18-73Y)	SRI Response at Week 52 (≥4 point reduction from baseline in SS score and no worsening in PGA and no new BILAG 1A/2B)
HGS1006-C1057/ BEL110752 m5	90 centers in 13 countries across 3 regions: Asia Pacific, Latin America, and Europe	May 2007 Completed: May 2009 865/810	To evaluate the efficacy, safety, tolerability, and impact on quality of life of IV belimumab in subjects with SLE	MC, R, DB, PC	Active SLE disease defined as SS disease activity score ≥6, stable SLE treatment regimen, positive ANA/ anti-dsDNA	Placebo or Belimumab 1 or 10 mg/kg on Days 0, 14, 28, and every 28 days thereafter; IV infusion; 52 weeks	Placebo: 287/226 IV Belimumab 1 mg/kg: 288/240 10 mg/kg: 290/241	821F 44M 35.5Y (18-71Y)	SRI Response at Week 52 (≥4 point reduction from baseline in SS score and no worsening in PGA and no new BILAG 1A/2B)

Protocol No. Location of Study Report (when applicable)	No. Study Centers Location(s)	Study Start; Enrollment Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender F/M; Mean Age (Range)	Primary Endpoint(s)
Other Efficacy and Safety Studies in Adult Subjects with SLE (IV Administration)									
LBSL02 Previously included in IV Belimumab application	59 centers in the USA (58) and Canada (1)	Oct 2003 Completed: Jun 2006 449/412	To evaluate the safety, tolerability and efficacy of IV belimumab, administered in addition to standard therapy, in subjects with SLE	MC, R, DB, PG, PC	Active SLE disease defined as SS disease activity score ≥4 at screening, stable SLE treatment regimen and history of measurable autoantibodies	Placebo or IV Belimumab 1, 4, or 10 mg/kg on Days 0, 14, 28 and every 28 days thereafter 52-week placebo controlled treatment phase and 24-week OL extension phase (IV Belimumab 10 mg/kg) Total 76 weeks	Placebo: 113/93 IV Belimumab 1 mg/kg: 114/87 4 mg/kg: 111/94 10 mg/kg: 111/90	419F 30M 42.2Y (20-75Y)	Co-primary endpoints: Percent change in SS disease activity score at Week 24. Time to the 1st mild/moderate or severe flare (as defined by the SLE Flare Index) over 52 weeks.

ANA=antinuclear antibody; anti-dsDNA=anti-double stranded deoxyribonucleic acid; BILAG= British Isles Lupus Assessment Group; DB=double-blind; F=female; IV=intravenous; M=male; MC=multicenter; OL=open-label; PC=placebo-controlled; PG=parallel group; PGA=Physician's Global Assessment; R=randomized; SLE=systemic lupus erythematosus; SS=SELENA SLEDAI; Y=years
Note: All data provided are from the ITT Populations.

2.3.2. Pharmacokinetics

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

Methods

Plasma concentrations of belimumab in were collected in 53 Paediatric SLE subjects (study BEL114055 Part A) and analysed with a population PK analysis. Subjects were enrolled into one of three cohorts: Cohorts 1 and 3 for ages between 12 and 17 years; Cohort 2 for ages between 5 and 11 years. Subjects received a weight-normalized belimumab dose of 10 mg/kg, administered on Days 0, 14 and 28, and every 28 days thereafter for 52 weeks. Pharmacokinetic samples were taken on the day of dosing (Days 0, 14, 28, 56, 168 and 364). For Cohorts 1 and 2, additional PK samples were taken following the first 2 doses for a more accurate assessment of the PK. Observed belimumab profiles are visualised in Figure 1, Figure 2, and Figure 3. Of the 53 subjects included in the analysis data set, 49 subjects were female and no subjects had proteinuria greater than 2 mg/mg or tested positive for immunogenicity. The study population is further described in Table 2.

Figure 1 Observed Median Belimumab Concentrations (ug/mL): Cohort 1 (Part A)

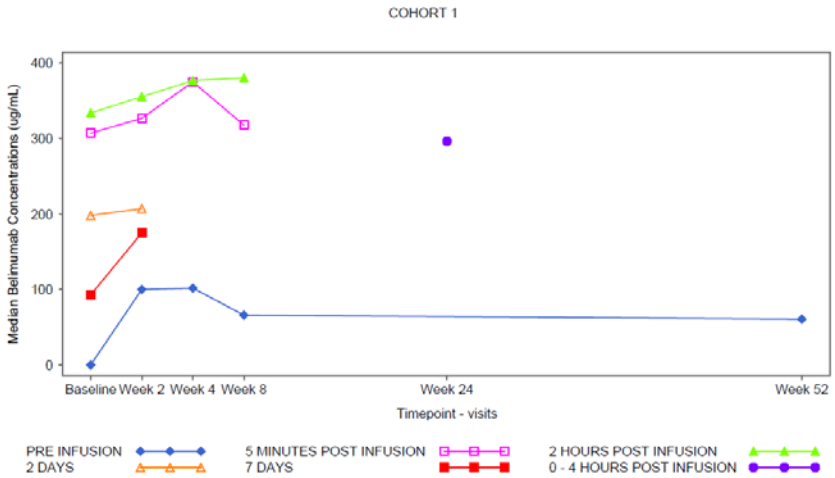


Figure 2 Observed Median Belimumab Concentrations (ug/mL): Cohort 2 (Part A)

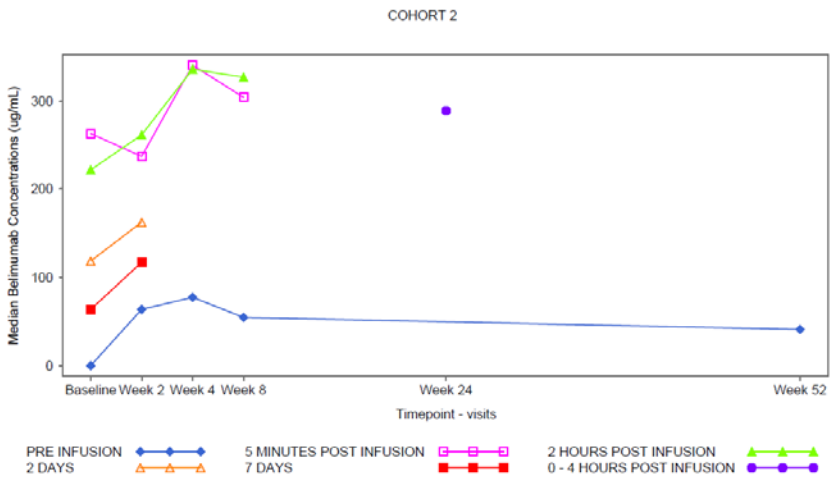


Figure 3 Observed Median Belimumab Concentrations (ug/mL): Cohort 3 (Part A)

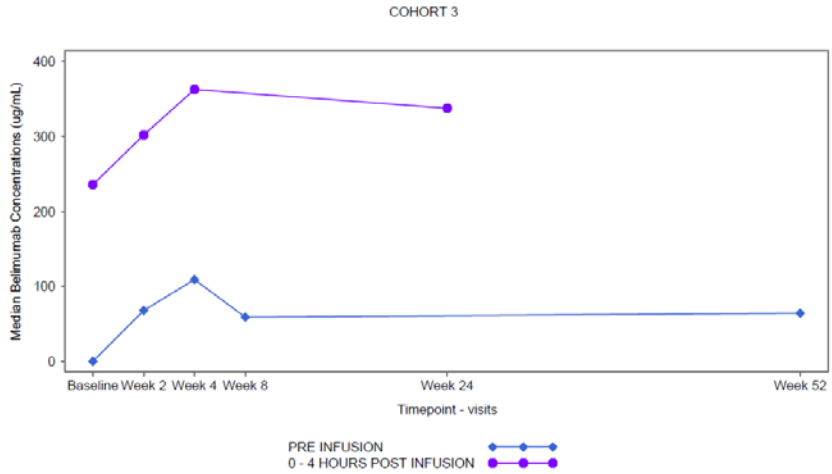


Table 2 Baseline Subject Characteristics by Cohort

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)

Source: Exploratory_Analysis.v3.csv
Abbreviations: BLyS=B-lymphocyte stimulator; BMI=body mass index; eGFR=estimated glomerular filtration rate
* Subject was 17 years of age at screening

Overall Modelling 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 Paediatric population. In the first instance, the adult model without further modification was used to evaluate the Paediatric PK, with the population parameters fixed at their adult derived estimates (MAXEVAL=0 argument in NONMEM). The implementation of the covariate effects in the adult model were then updated to be consistent with the Paediatric covariate distributions, and the population parameters re-estimated for the Paediatric population (Step 1). The full covariate model approach [Gastonguay, 2011] 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).

Data handling

Pre-first dose records were excluded from the analysis (one detectable sample of 0.648 µg/mL). Samples below limit of quantification were excluded (one sample). Nine post-first dose samples, which were not analyzed (NA) were also excluded.

Model Development and Evaluation

All data manipulation, model development and analysis were performed with NONMEM version 7.3, PsN version 4.6.0 and R version 3.2.5. The first-order conditional estimation method with interaction (FOCE-I) in NONMEM v7.3 was used to estimate the parameters of the population PK model, and the likelihood ratio test was used to determine whether the drop in objective function was sufficiently large to justify the addition of model parameters. For the addition of a single degree of freedom, such as a single covariate parameter, the likelihood ratio test requires a drop of at least 3.84 objective function points for this extra parameter to be considered significant at the 5% level of uncertainty.

Basic goodness-of-fit plots and visual predictive checks were used for model evaluation.

Covariate analysis

The importance of each covariate on determining the PK was quantified based on a variation of the full covariate model method of Gastonguay [Gastonguay, 2011], with covariate inclusion criteria based on pharmacokinetic relevance and statistical significance as outlined below. The ratio of the model parameter at the 10^{th} and 90^{th} percentiles of the covariate, relative to the model parameter at the median covariate value (denoted R_{10} and R_{90}, respectively) was chosen as a quantifiable measure of the pharmacokinetic relevance of the covariate effect accounting for the width of the distribution of the underlying covariate values.

- A covariate was considered pharmacokinetically relevant if either ratio R_{10} or R_{90} was less than 0.8 or greater than 1.25 - the same thresholds used for bioequivalence studies.
- If both R_{10} or R_{90} were within the 0.8 to 1.25 domain, the 95% confidence interval (CI) about each estimate was calculated from the uncertainty in the covariate parameter. If the 95% CIs about each ratio remained inside the 0.8 to 1.25 domain, the covariate was considered irrelevant from a pharmacokinetic perspective and not retained.

o If the 95% CI of the covariate parameter crossed zero, the covariate could not be classified as being positively or negatively correlated with the model parameter with at least 95% certainty. In this case the covariate was considered irrelevant from a pharmacokinetic perspective and not retained.

- If the 95% CI of the covariate parameter was wholly positive or negative then covariate was classified as potentially relevant from a pharmacokinetic perspective and retained.

The following covariates were tested in the Paediatric study population: proteinuria, body weight, BMI, fat-free mass, age, baseline BLyS, baseline C-reactive protein, baseline anti-double stranded DNA antibody, baseline complement C3, baseline complement C4, naïve B cells, baseline SELENA-SLEDAI score, baseline total bilirubin, baseline alanine aminotransferase, baseline aspartate aminotransferase, race, ethnicity, baseline co-medications (immunosuppressant, azathioprine, methotrexate, mycophenolate, anti-malarial, NSAID, aspirin).

Results

The Paediatric population PK model development was guided by the model structure and covariate effects identified in the adult IV population PK analysis [Struemper 2013]. The adult PK model was two compartmental with first-order elimination, and between-subject variability on CL, V1, and V2 parameters. Residual variability was characterized using a combined proportional and additive model. In the first instance the adult population PK model was used to characterize the Paediatric PK, without modification or re-estimation of the model parameters, and the fit to the individual observations was reasonable. Subsequently, the model parameters were re-estimated. The categorical proteinuria covariate included in the adult model was replaced with the continuous measure of proteinuria at baseline (BPROT), and body size was accounted for with allometric scaling on fat-free mass (BFFM) on all model parameters.

The final model was a linear two compartment model with first-order elimination, with typical estimates of clearance (158 mL/day), steady-state volume of distribution (3549 mL or approximately 3.5 L) (Table 3), and distribution and terminal half-lives of 0.8 and 16.3 days respectively. Shrinkage on the between-subject random variables was reasonable at 9.63% (CL), 11.72% (V1) and 20.25% (V2). The individual (IPRED) and population (PRED) model predictions matched the observed data, with the conditional weighted residuals uniform and unbiased with respect to time and IPRED (Figure 4). A visual predictive check of the serum concentration versus nominal time, based on 1000 simulations of the paediatric dataset, confirms that the between-subject variability predicted by the model is consistent with the spread observed in data (Figure 5). Bootstrap estimates were consistent with the final model estimates (Table 3).

Table 3 Population Parameter Estimates for the Final PK Model

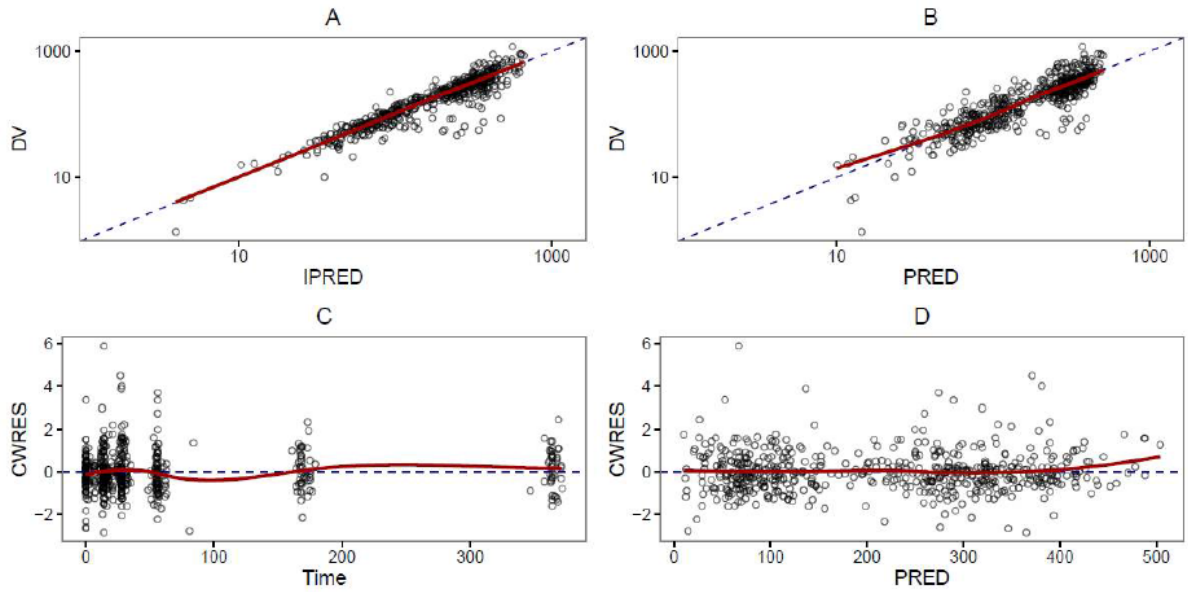
Parameters	Model Point estimate (%RSE, 95% CI)	Bootstrap[a] Median (95% CI)
Fixed effects		
CL (mL/day)	158 (3.62%, 147-169)	157 (142-169)
x (BFFM/34.4)$^{\theta}$	0.691 (18.6%, 0.439-0.942)	0.691 (0.418-0.963)
x (BEGFR/105.21)$^{\theta}$	0.561 (34.4%, 0.183-0.939)	0.510 (0.079-0.966)
x (BIGG/14.5)$^{\theta}$	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

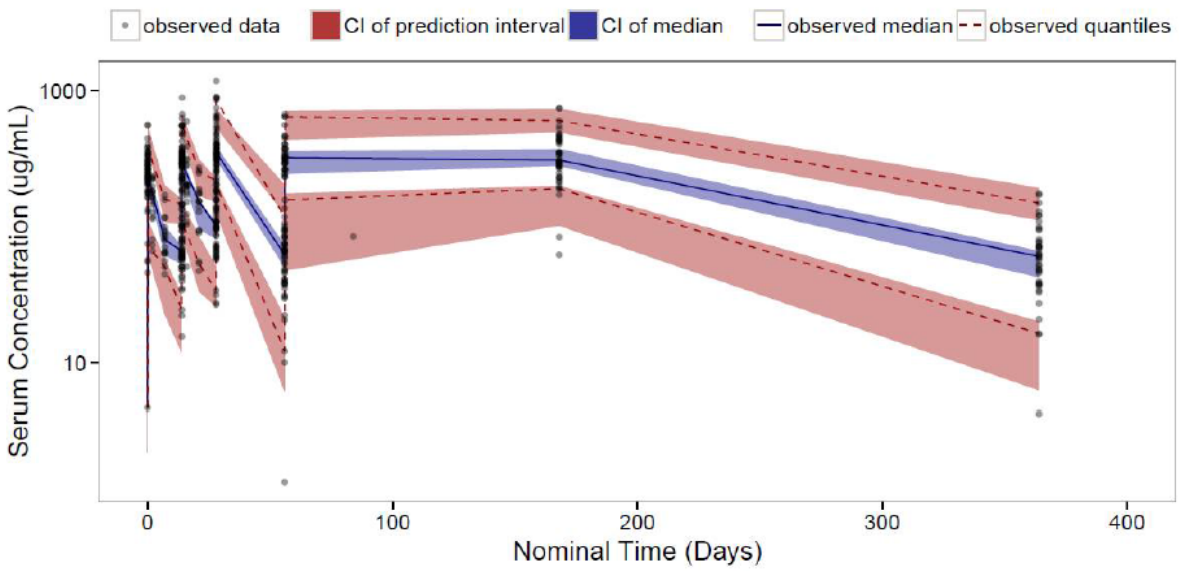
a. Bootstrap parameters based on 1694 successful minimizations (out of 2000 attempts)

Figure 4 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.

Figure 5 Visual predictive check of the final model with respect to nominal time

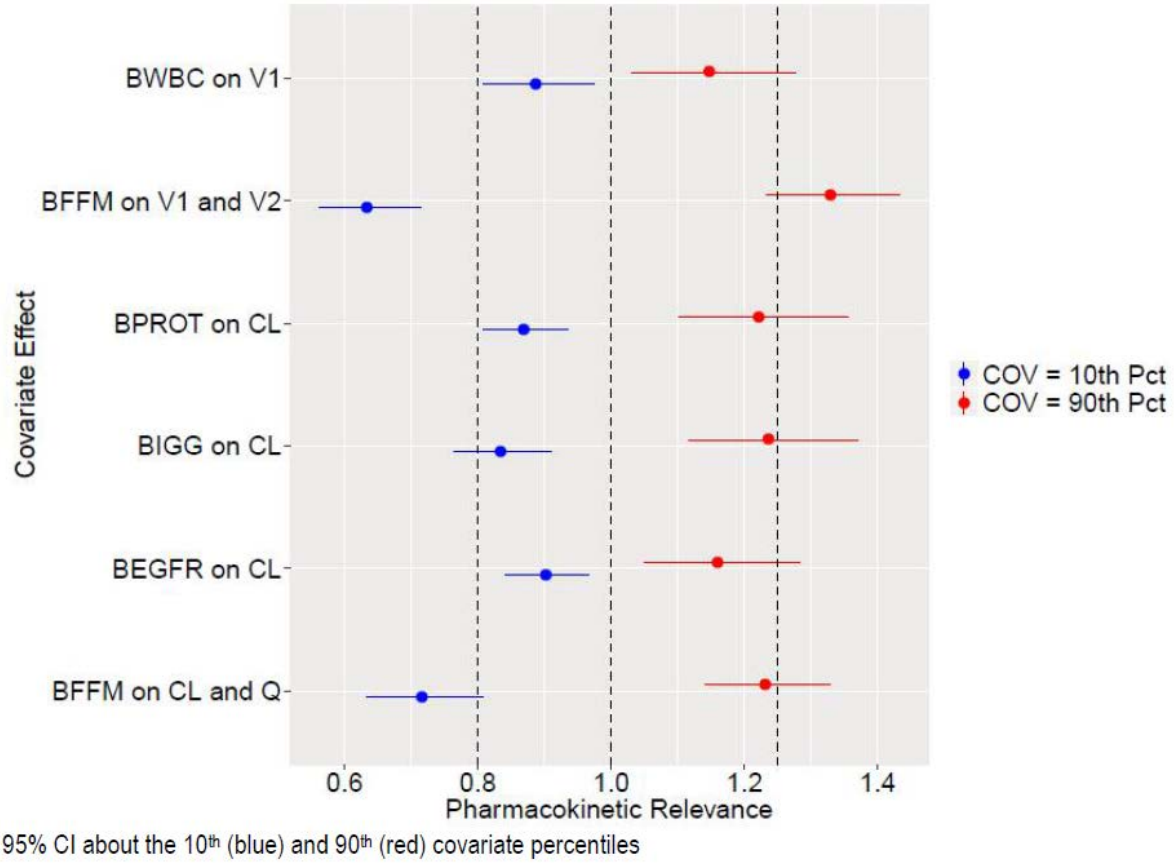


Observed data (black points), observed 2.5th and 97.5th percentiles (dotted red line) with simulated 95% CI (shaded red regions); observed 50th percentile (solid blue line) with simulated 95% CI (shaded blue region).

Effects of body size on the population PK parameters were best characterized in terms of fat-free mass; age did not have a statistically significant effect on clearance after accounting for body size effects. Additional statistically significant covariate effects retained in the final model were baseline white blood cell count on the central volume of distribution (V1) and baseline immunoglobulin G (IgG), proteinuria, and estimated glomerular filtration rate on central clearance. At the 10th and 90th percentiles of the

corresponding covariate distribution, none of the point estimates for these additional covariate effects exceeded an effect range of 0.8 to 1.25 (Figure 6), i.e., even towards the extremes of the covariate values, the effects on the affected PK parameters were relatively minor. Other covariate effects included in the adult IV population PK model [Struemper, 2013] did not satisfy the inclusion criteria and were omitted from the final paediatric model.

Figure 6 Pharmacokinetic relevance of the covariate effects of the final PK model.



Where 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.

Additional covariates of clinical interest applied to central clearance in the final model such as baseline liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin), baseline parameters related to disease activity (SELENA-SLEDAI score, B-lymphocyte stimulator (BLyS) concentration, C-reactive protein [CRP] concentration), comedications and race categories (Asian, Black) were not statistically significant. Hispanic ethnicity was found to be a statistically significant covariate of clearance. However, the effect was small with negligible impact on the model's fit to the data and was not added to the final model.

All pre-dose PK samples were excluded from the analysis; however, one sample was above limit of quantification. Clarification was sought during the review on the reason for a pre-dose concentration of belimumab, and how the post-dose samples from this patient were handled. The MAH provided a description of the data handling for the individual with a positive pre-dose sample, where the post-dose PK samples have been included in the analysis. The CHMP agreed that the individual time profile for this subject demonstrates a good fit with no indications of an erroneous dose. The use of the post-dose PK samples was therefore endorsed by the CHMP.

Pharmacokinetics in the paediatric patient population

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 [Report HGS1006-POPPK]. Steady-state exposure parameters Cmax, Cmin, Cavg, 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 Paediatric age groups and the overall Paediatric population are consistent with the adult exposure parameters with largely overlapping confidence intervals. PK parameters CL and Vss are slightly lower for the younger compared to the older age group and the same parameters for both Paediatric age groups are lower than parameters for adults as expected from the allometric effect of body size on clearance and volume of distribution.

Table 4 Summary of individual belimumab PK and 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
Vss (mL)	Geo. Mean (%CV)	2542 (47.7%)	3798 (35.7%)	3521 (41.3%)	5216 (12.6%)
	95% CI	1921 - 3365	3425 - 4212	3164 - 3918	5163 - 5271
	Range	1246 - 5620	1383 - 6782	1246 - 6782	2163 - 8653
CL (mL/day)	Geo. Mean (%CV)	119 (33.1%)	169 (39.4%)	158 (40.8%)	232 (33.1%)
	95% CI	97 - 145	151 - 190	143 - 176	226 - 239
	Range	73 - 203	75 - 480	73 - 480	69 - 623
T1/2,α (Days)	Geo. Mean (%CV)	0.73 (34.4%)	0.81 (32.0%)	0.79 (32.4%)	1.68 (13%)
	95% CI	0.6 - 0.9	0.74 - 0.89	0.73 - 0.86	1.66 - 1.7
	Range	0.42 - 1.29	0.39 - 1.39	0.39 - 1.39	0.75 - 2.57
T1/2,β (Days)	Geo. Mean (%CV)	16.1 (30.2%)	16.4 (37.4%)	16.4 (35.8%)	18.0 (27.3%)
	95% CI	13.4 - 19.3	14.7 - 18.3	14.9 - 18	17.6 - 18.4
	Range	11.4 - 29.8	7.7 - 39.3	7.7 - 39.3	6.3 - 39.6

Source: Posthoc_Analysis.Mod071.ReportTable.csv

Abbreviations: %CV= coefficient variation: $\sqrt{e^{variance}-1}$; 95% CI= 95% CI of the geometric mean

Table 5 summarise the PK and exposure parameters by body weight. Values between categories are similar with largely overlapping 95% CIs and a weak trend towards increased values for increased body weight.

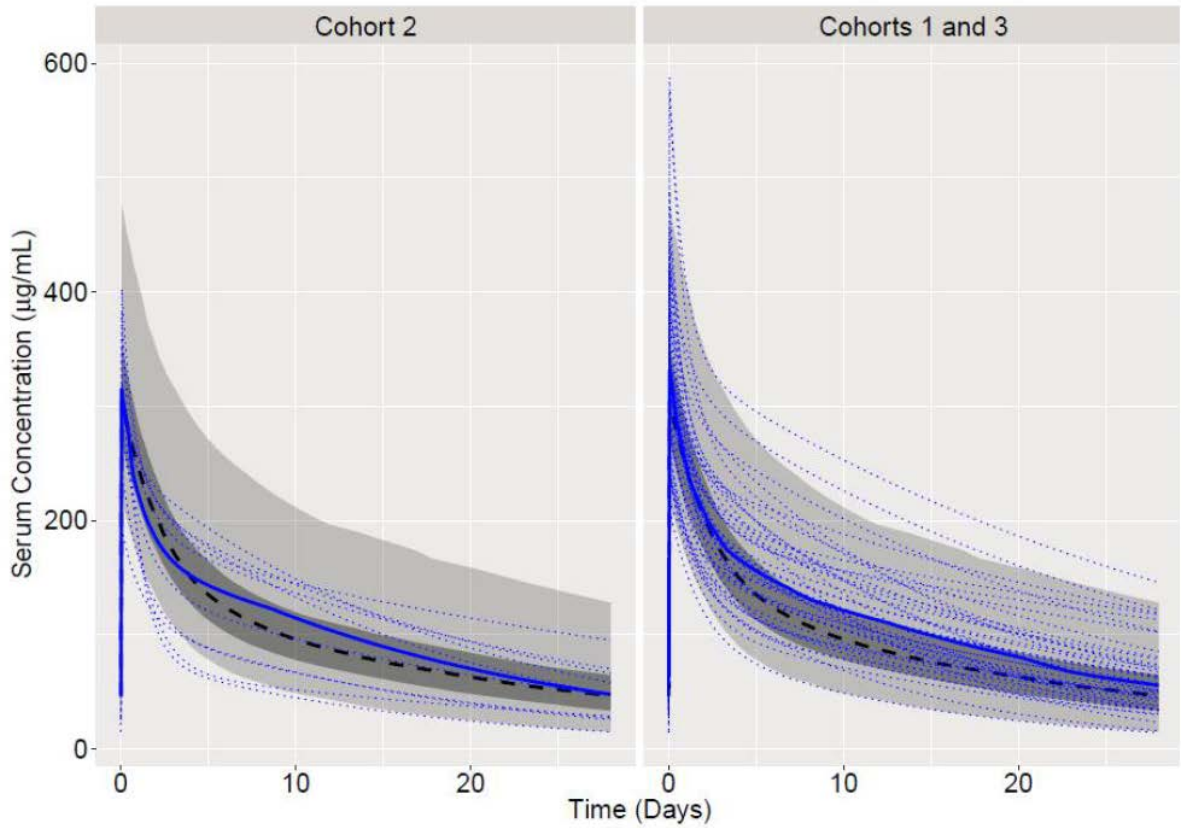
Table 5 Belimumab Exposure and PK Parameters in IV Belimumab Phase 2 Paediatric Study (BEL114055, Part A) by Body Weight Quartile

Parameter	Summary	Quartile 1 < 38.7 kg N=13	Quartile 2 (≥ 38.7 to < 52.3) kg N=13	Quartile 3 (≥ 52.3 to < 67) kg N=13	Quartile 4 ≥ 67 kg N=14
Cmax,ss (µg/mL)	Geo. Mean (%CV)	304 (24.7%)	307 (21.2%)	283 (45.4%)	369 (25.3%)
	95% CI	266 - 347	274 - 344	224 - 358	324 - 420
	Range	193 - 408	241 - 488	81 - 576	211 - 587
Cmin,ss (µg/mL)	Geo. Mean (%CV)	45 (65.2%)	52 (37.4%)	46 (110.6%)	58 (59.8%)
	95% CI	33 - 63	43 - 64	28 - 75	43 - 77
	Range	15 - 119	30 - 118	4 - 146	14 - 122
Cavg,ss (µg/mL)	Geo. Mean (%CV)	97 (44.2%)	108 (22.3%)	100 (62.3%)	126 (37.1%)
	95% CI	77 - 122	96 - 122	73 - 137	104 - 152
	Range	49 - 177	78 - 166	21 - 238	50 - 208
AUC,ss (day µg/mL)	Geo. Mean (%CV)	2713 (44.2%)	3029 (22.3%)	2808 (62.3%)	3525 (37.1%)
	95% CI	2156 - 3414	2687 - 3415	2057 - 3832	2920 - 4255
	Range	1381 - 4960	2197 - 4647	589 - 6654	1396 - 5838
Vss (mL)	Geo. Mean (%CV)	2493 (43.9%)	3489 (34.7%)	3837 (32.5%)	4517 (28%)
	95% CI	1985 - 3132	2905 - 4190	3230 - 4559	3912 - 5217
	Range	1246 - 4642	1685 - 6002	2002 - 6292	2962 - 6782
CL (mL/day)	Geo. Mean (%CV)	112 (36.6%)	150 (28.5%)	173 (34.3%)	212 (32.9%)
	95% CI	92 - 136	129 - 175	144 - 207	179 - 251
	Range	73 - 203	91 - 229	79 - 291	146 - 480
T1/2,α (days)	Geo. Mean (%CV)	0.7 (33.6%)	0.83 (31.3%)	0.83 (36.6%)	0.81 (28.3%)
	95% CI	0.59 - 0.84	0.71 - 0.99	0.69 - 1.01	0.7 - 0.94
	Range	0.42 - 1.16	0.41 - 1.36	0.39 - 1.39	0.55 - 1.36
T1/2,β (days)	Geo. Mean (%CV)	16.6 (37.4%)	17 (36.7%)	16.2 (41.8%)	15.7 (31.4%)
	95% CI	13.6 - 20.2	14 - 20.7	13 - 20.2	13.4 - 18.4
	Range	11.4 - 39.3	9.1 - 37	7.7 - 29.8	10.2 - 30.1

Steady-state PK profiles for all belimumab-treated paediatric subjects in study BEL114055 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 7. Almost all paediatric profiles are completely contained in the adult 95% prediction interval; the median paediatric profiles are consistent with the median adult profiles.

In summary, the PK results indicated that body-weight proportional dosing resulted in similar exposures across the body size and age range in the studied paediatric population, and between paediatric and adult subjects with SLE.

Figure 7 Simulated Steady-State PK Profiles in IV Belimumab Phase 2 Paediatric Study (BEL114055, Part A, by Age Group) and Pivotal Phase 3 Adult Studies (C1056 and C1057)



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.

2.3.3. Pharmacodynamics

Mechanism of action

The MAH states that pharmacodynamic responses to belimumab in Paediatric patients were consistent with the proposed mechanism of action of neutralizing BLyS, a B cell survival factor that inhibits B cell apoptosis and stimulates the differentiation of B cells into immunoglobulin producing plasma cells.

Paediatric B cell and immunoglobulin responses are compared in Table 6 with corresponding responses from the belimumab IV pivotal trial C1056. Naïve B cells, which among the tested B cell subsets are most sensitive to BLyS neutralization, also responded very similar between adult and Paediatric subjects. Memory B cells had a lesser increase for Paediatric as compared to adult patients at Week 52, contributing to the slightly higher reduction in overall B cells observed in the Paediatric compared to the adult population.

Also for the rare B cells subsets with small serum cell counts (activated, plasmacytoid and SLE subset B cells; plasma and short-lived plasma cells), responses were consistent between the Paediatric and adult 10 mg/kg groups, except for the smaller reduction in plasmacytoid B cells for Paediatric patients. Larger differences were observed when comparing Paediatric and adult placebo groups, with increases observed for the Paediatric placebo group compared to relatively minor changes in the adult placebo group.

Comparisons with adult results need to be interpreted with caution due to the large between-subject variability of B cell measurements, especially for these less frequent B cell and plasma cell subsets, and the small Paediatric subject numbers.

Median percent changes from baseline at Week 52 for serum immunoglobulins were similar between Paediatric and adult populations (Table 6). Median percent changes from baseline at Week 52 for anti-dsDNA autoantibodies and complement C3 and C4 in response to 10 mg/kg belimumab were similar between Paediatric and adult SLE patients (data not shown here).

The MAH concludes that B cell and plasma cell, as well as immunoglobulin and SLE biomarker responses were consistent between Paediatric and adults SLE patients receiving 10 mg/kg IV belimumab.

Table 6 Median Percent Change from Baseline in Biomarkers at Week 52 in IV Belimumab Phase 2 Paediatric 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

Source: CSR C1056 Final TE23.1_W76 -TE23.3_W76, TE29.1_W76 -TE29.9_W76; CSR BEL114055 Table 4.1, Table 4.8

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+/"

Some important differences were noted by the CHMP in the pharmacodynamics response. In placebo-treated subjects, the median percent change from baseline for some biomarkers differs widely between children (BEL114055) and adults (C1056), for example activated and plasmacytoid B cells. The MAH was asked to discuss these findings, and whether these differences are of importance for the extrapolation to children. The MAH clarified that these rare B cell subsets had a large variability in the Benlysta clinical development plan, and that the observed differences could be due to the small number of cases included in the paediatric study. This CHMP considered the response acceptable.

2.3.4. PK/PD modelling

A post-hoc, exploratory exposure-response analysis was conducted to assess any impact of between-subject exposure variability on clinical response at Week 52 in the 10 mg/kg group of the Paediatric study BEL114055. The analysis demonstrated relatively flat exposure-response characteristics for clinical responses within the tested 10 mg/kg dose level based on exposures quantified by steady-state Cavg, Cmax, and Cmin. SLE Responder Index responders had a similar median exposure than non-responders; both groups showed large overlap between exposures (Figure 8). Similarly, subjects who had a serious adverse event (SAE) any time during Part A had a similar median exposure than subjects who had no SAE; both groups showed large overlap between exposures (Figure 9). Also naïve B cells (Figure 10), a key pharmacodynamic response variable, or biomarkers for clinical response such anti-dsDNA antibodies (Figure 11) had relatively flat exposure response curves.

Figure 8 SRI Response at Week 52 versus Belimumab Cavg in IV Belimumab Phase 2 Paediatric Study (BEL114055, Part A)

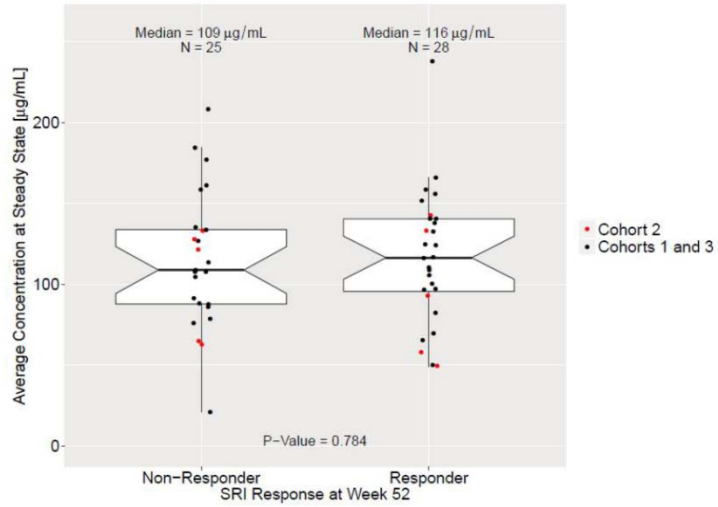


Figure 9 Serious Adverse Events versus Belimumab Cavg in IV Belimumab Phase 2 Paediatric Study (BEL114055, Part A)

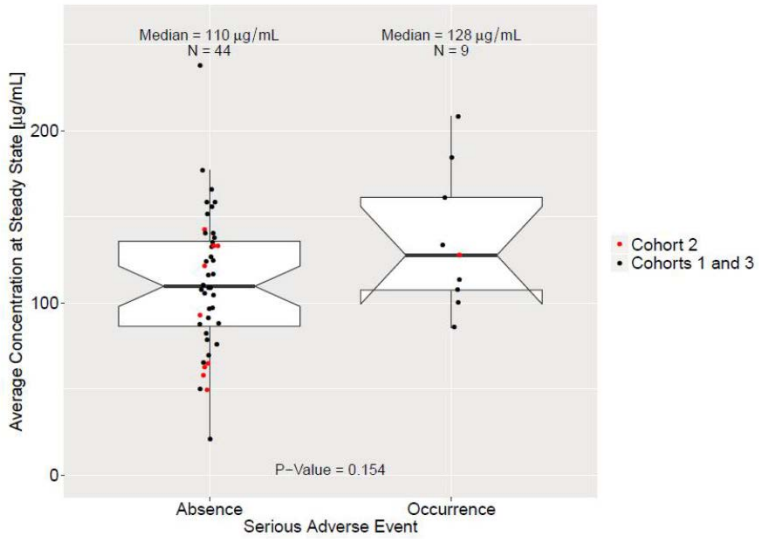


Figure 10 Naïve B Cell Response at Week 52 versus Belimumab Cavg in IV Belimumab Phase 2 Paediatric Study (BEL114055, Part A)

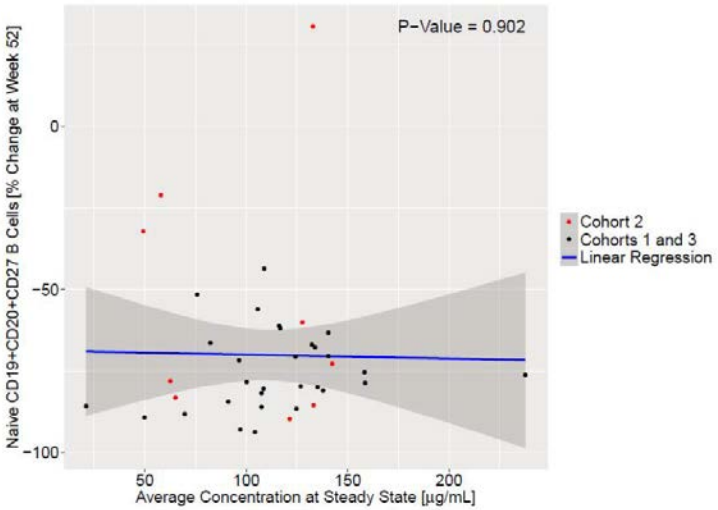
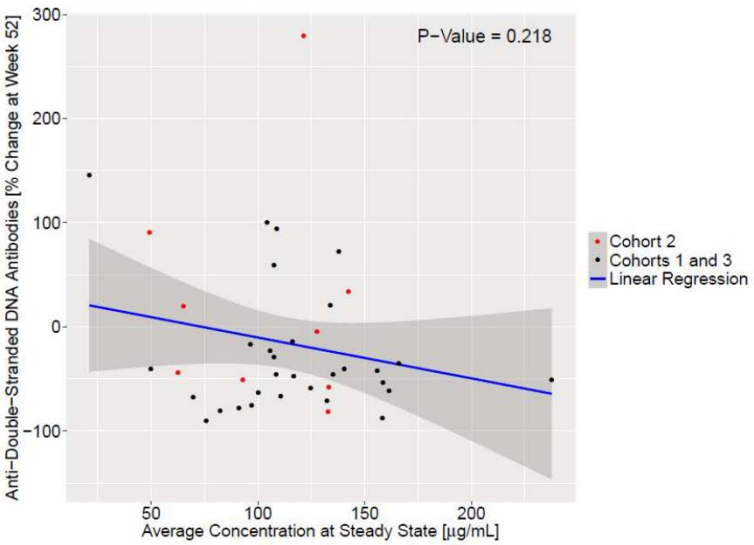


Figure 11 Anti-dsDNA Antibody Response at Week 52 versus Belimumab Cavg in IV Belimumab Phase 2 Paediatric Study (BEL114055, Part A)



These exposure-response results for the BEL114055 Paediatric study population are consistent with prior clinical experiences in adult SLE patients. In the two pivotal belimumab IV Phase 3 trials C1056 and C1057 there was no apparent safety dose-response, only a relatively flat efficacy dose-response, and for most biomarkers little or no difference between the responses to the 1 or 10 mg/kg doses [Furie, 2011; Navarra, 2011; Stohl, 2012]. Similarly, in the belimumab SC Phase 3 trial BEL112341 (weekly 200 mg belimumab) there was no apparent efficacy, safety or biomarker exposure-response [Struemper, 2018].

The combination of these exposure or dose-response results indicates that at IV 10 mg/kg every four weeks or at SC 200 mg every week dose levels, the functional relationship between BLyS neutralization and belimumab exposure is in a saturated phase at near maximal BLyS neutralization.

2.3.5. Discussion on clinical pharmacology

Belimumab concentrations were collected in 53 Paediatric SLE subjects (study BEL114055, part A) and analysed with a population PK analysis. PK samples were measured on the day of dosing (Days 0, 14, 28, 56, 168, and 364) and a minimum of 6 samples per individual were collected. The belimumab 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 Paediatric population. Structural model parameters and covariate effects were estimated using paediatric data only.

A population PK analysis was performed on the paediatric PK data with the aim to compare paediatric and adult belimumab exposure to support the extrapolation of efficacy and safety of adult Benlysta results. In general, the analysis is well performed. In the adult model, body weight was a covariate on both the CL and V1, scaling positively with both parameters. Body mass index was also an additional covariate on V1 with a negative correlation; that is, a larger BMI was associated with a smaller central volume. The fat-free mass may be a better predictor of clearance and volume, and this BMI correction to volume may account for subjects who have a typical body weight but a large BMI, and therefore a smaller fat-free mass. This modification seems reasonable and is acceptable.

The covariate analysis was questioned by the CHMP as it was not fully understood why a covariate analysis have been performed in the paediatric population if the expectation is that the pharmacology is the same in adults and children. Results of the predictions from the reference adult model were not submitted and hence it was not possible to evaluate whether it would have been sufficient to use the paediatric predictions as such. In the response, the MAH provided documentation for the initial runs with the adult model and it was clear that adult model did not provide accurate paediatric predictions, and hence re-estimation on the paediatric data was considered acceptable by the CHMP. The following covariate effects, included in the adult population PK model, were not relevant from a PK perspective for paediatrics: albumin on CL; administration of an ACE-inhibitor or steroid on CL; haemoglobin levels as a covariate on V1. These four covariate effects were removed from the paediatric PK model. As the paediatric sample size is somewhat small to be able to draw firm conclusions on the covariate analysis [Ribbing and Jonsson, 2004], the MAH was asked during the evaluation to provide model predictions with the excluded covariates in the model. From a pharmacological reasoning, it was not understood why for example albumin and haemoglobin are not predictors of PK in the paediatric population when that is the case in the adult population. In response, the MAH provided reasoning that the removed covariates were not statistically significant predictions for the paediatric data. Furthermore the albumin and haemoglobin levels measured in the paediatric data would not lead to clinically meaningful changes in PK. The CHMP agreed that from a purely predictive purpose the PK model is adequate. However, in future analyses, the MAH is recommended to keep pharmacologically plausible covariates in the paediatric model.

The final model seems to describe the paediatric data reasonably well; however, the MAH was asked to provide a visual predictive check with Concentration versus Time after dose for clarity. The exposure versus body weight graphs provided by the MAH indicated that the median belimumab concentration in the paediatric population is in general somewhat higher than in the adult population although the exposure range in both indications are largely overlapping. However, since no apparent exposure-safety relationship has been detected for serious adverse events or serious infections the exposure range in the paediatric population is acceptable and the proposed dosing regimen of 10 mg/kg to all SLE patients was endorsed by the CHMP.

In study BEL114055, the pharmacodynamic response was consistent with the adult data.

An exploratory exposure-response analysis has been provided where no apparent exposure-response relationship could be detected. These results are similar to the findings in the adult SLE population and could potentially be interpreted as that maximum response has been reached. However, a limitation of the analysis is based on one dose level which means that the exposure relation cannot be distinguished from other factors influencing the response and should as such be interpreted with caution. Due to the limited dose-ranging information in the Paediatric study, additional exposure-response analyses on this study data are not foreseen to be informative.

The steady-state exposure parameters Cmax, Cmin, Cavg, and AUC were similar between the age and weight groups with a trend towards slightly higher exposure in the older compared to the younger age group. Exposure parameters for both Paediatric age groups and the overall Paediatric population were consistent with the adult exposure parameters with largely overlapping confidence intervals. Geometric mean Cmax,ss=305/317/311 [µg/mL] and AUC=2569/3126/2811 [day µg/mL] in 5-11 years old, 12-17 years old, and adults, respectively. Cmin were 2569 [day µg/mL] in the 5- to 11-year-old-group, and 3126 [day µg/mL] in the 12- to 17-year-old-group.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetic parameters are based on individual parameter estimates from a population pharmacokinetic analysis of 53 patients from a study in paediatric patients. Following intravenous administration of 10 mg/kg on Days 0, 14 and 28, and at 4 week intervals thereafter belimumab exposures were similar between paediatric and adult SLE subjects. Steady-state geometric mean Cmax, Cmin, and AUC values were 305 µg/mL, 42 µg/mL, and 2569 day.µg/mL in the 5- to 11-year-old-group, and 317 µg/mL, 52 µg/mL, and 3126 day.µg/mL in the 12- to 17-year-old-group (n=43).

The belimumab population PK model for the Paediatric population adequately described the data. The median exposure in paediatrics is slightly higher compared to adults. However no apparent exposure-safety relationship has been detected for serious adverse events or serious infections, either in the paediatric or adult population; therefore the exposure range in the paediatric population is acceptable and the proposed dosing regimen of 10 mg/kg to all SLE patients was endorsed by the CHMP.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies have been performed in children which was considered acceptable to the CHMP.

2.4.2. Main study

BEL114055: Double-Blind Trial to Evaluate the Safety, Efficacy, and Pharmacokinetics of Belimumab, a Human Monoclonal Anti- BLyS Antibody, Plus Standard Therapy in Paediatric Patients with Systemic Lupus Erythematosus (SLE)

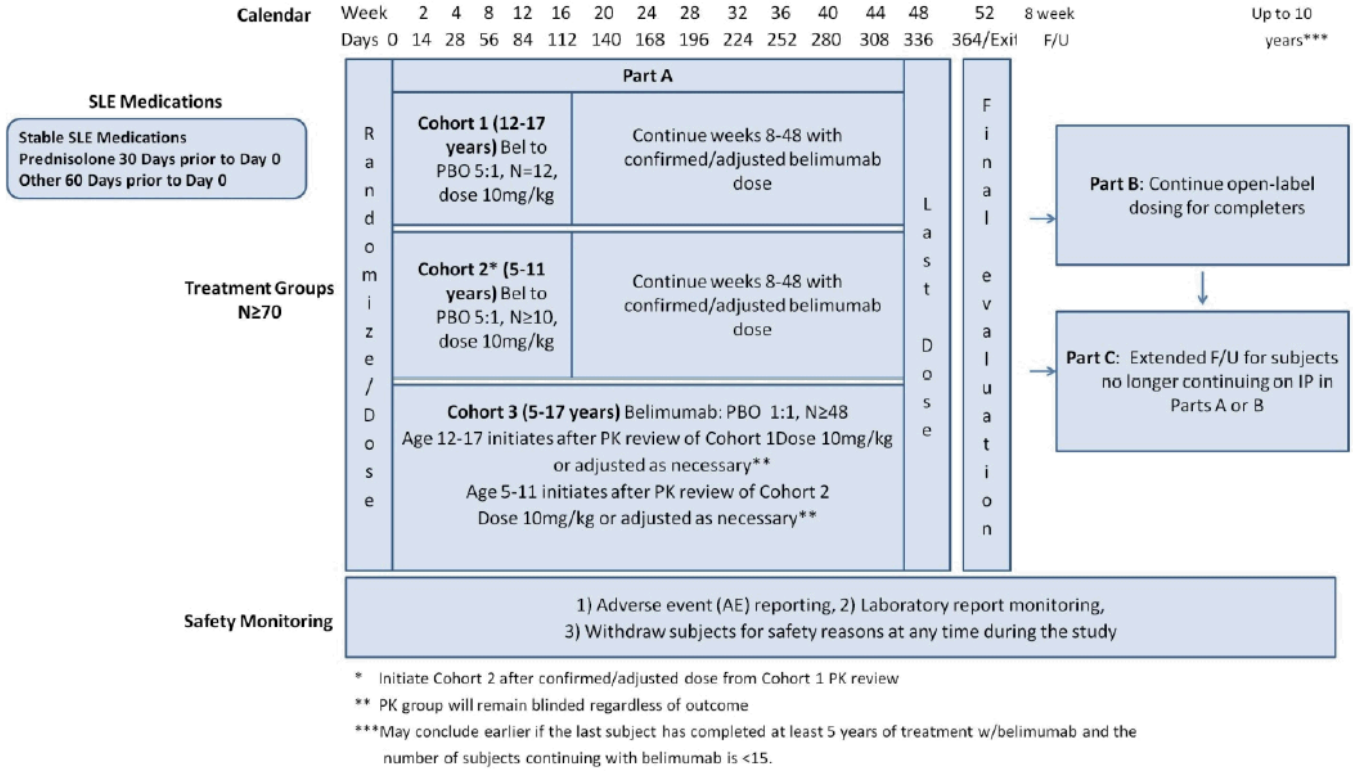
Methods

BEL114055 was a multi-centre study to evaluate the safety, efficacy and PK of belimumab plus background standard therapy in at least 70 paediatric subjects 5 years to 17 years of age with active SLE. The study consists of three separate phases:

- Randomized, placebo-controlled, double-blind 52-week treatment phase (Part A)
- Long term belimumab open label safety follow up for any subject who completes Part A (Part B)
- Long term safety follow-up phase for subjects who withdraw from Part A or Part B at any time (Part C)

A schematic of the study is provided in Figure 12.

Figure 12. BEL114055 Study Schematic



Study participants

Eligible subjects were 5 to 17 years of age and had clinically active SLE disease, defined as a SELENA SLEDAI disease activity score of ≥6 at screening. Subjects had to have 4 or more of the 11 American College of Rheumatology (ACR) criteria for the classification of SLE either at screening or in the past. Subjects also had to have an unequivocally positive test result for anti-nuclear antibody (ANA) titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL serum antibody either from 2 independent time points within the study screening period or 1 positive historical test result and 1 positive test result during the screening period.

Subjects were to be on a stable SLE treatment regimen at a fixed dose for at least 30 days prior to Day 0 inclusive of any of the following (alone or in combination): corticosteroids (prednisone or prednisone equivalent up to 0.5 mg/kg/day), antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDs), or any other immunosuppressive or immunomodulatory therapy including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil [MMF], mycophenolate mofetil hydrochloride, and mycophenolate sodium), calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, oral cyclophosphamide, 6-mercaptopurine, or thalidomide.

Key exclusion criteria included active central nervous system (CNS) lupus requiring therapeutic intervention within 60 days prior to Day 0; requiring renal replacement therapy (e.g., hemodialysis, peritoneal dialysis) within 90 days of Day 0 or currently on renal replacement therapy; an estimated glomerular filtration rate as calculated by Schwartz Formula of less than 30 mL/min; or acute severe nephritis defined as a significant worsening of renal disease (e.g., the presence of urinary sediments and other lab abnormalities) that, in the opinion of the study investigator, could have led to the subject requiring induction therapy with IV cyclophosphamide, MMF or high dose corticosteroids during the first 6 months of the trial. Other exclusion criteria included receipt of belimumab or any B cell targeted therapy at any time and receipt of specific treatments/therapy (e.g., abatacept, any biologic investigational agent, IV cyclophosphamide, anti-tumor necrosis factor [TNF], interleukin-1 receptor antagonist

[anakinra], IV immunoglobulin [IVIG], 3 or more courses of systemic corticosteroids, plasmapheresis, live vaccine) within protocol-defined timeframes prior to Day 0.

There are no important differences between the eligibility criteria in BEL114055 and the phase III studies in adults.

At the time of BEL114055 study initiation in late 2012, a SELENA SLEDAI score ≥8 at screening was required. This was intended to enrich the enrolled population as subjects with higher disease activity in the 2 pivotal adult IV studies demonstrated a greater treatment effect for belimumab vs. placebo as measured by the SRI (see below). However, due to continued enrolment difficulties, eligibility criteria were subsequently relaxed following protocol Amendment 04 by reducing the SELENA SLEDAI score required at screening to ≥6.

Treatments

Subjects in Cohort 1 and Cohort 2 were randomized in a 5:1 ratio and in Cohort 3, in a 1:1 ratio to 1 of 2 treatment groups:

- belimumab 10 mg/kg on Days 0, 14, 28 and then every 28 days through Week 48 of the blinded period for a total of 14 doses.

or

- placebo

In Cohort 3, randomization was stratified by age group (5-11 or 12-17 years at screening) and screening SELENA SLEDAI scores (6-12 vs. ≥13). (Note: the planned stratification included age group but no children in the younger age group were randomized to Cohort 3).

Concomitant treatment with azathioprine, mycophenolate mofetil, methotrexate and oral cyclophosphamide in restricted doses was allowed.

The total dose of systemic steroids could be increased as clinically required during the first 6 months of the trial, but must have returned to within 25% or 5 mg over the baseline dose, whichever was higher, by Week 24.

After Week 24, an increase > 25% or > 5 mg over the baseline dose, whichever is higher, for SLE activity deemed the subject a treatment failure.

Within 8 weeks before Week 52, no new increase over the baseline or Week 44 visit dose, whichever is higher, was allowed.

Objectives

The objectives of the study were to:

- Evaluate the safety and tolerability of belimumab in the Paediatric SLE population.
- Evaluate the pharmacokinetics (PK) of belimumab in the Paediatric SLE population.
- Evaluate the efficacy of belimumab in the Paediatric SLE population.
- Evaluate the effects of belimumab on the quality of life in the Paediatric SLE population.

Outcomes/endpoints

The primary efficacy endpoint was the SLE Response Index (SRI) response rate at Week 52.

A SRI response was defined as: ≥4 point reduction from baseline in SELENA SLEDAI score, AND no worsening (increase of <0.30 points from baseline) in PGA (Physician's Global Assessment), 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) .

The major secondary efficacy endpoints were:

1. 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

a. At least 50% improvement in any 2 of 5 endpoints below and no more than 1 of the remaining worsening by more than 30%

b. At least 30% improvement in 3 of 5 endpoints below and no more than 1 of the remaining worsening more than 30%

i. Percent change in ParentGA (Parent's Global Assessment) at Week 52

ii. Percent change in PGA at Week 52

iii. iii. Percent change in SELENA SLEDAI score at Week 52

iv. iv. Percent change in PedsQL physical functioning domain at Week 52

v. v. Percent change in 24 hour proteinuria at Week 52 (g/24hour equivalent by spot urine protein to creatinine ratio)

2. Proportion of subjects with a sustained SRI response, defined as having a response on the primary efficacy endpoint at Weeks 44, 48 and 52

3. Proportion of subjects with a sustained ParentGA response defined as having >0.7 improvement at Weeks 44, 48, and 52 compared to baseline

Among other secondary endpoints were time to first severe flare, time to first flare and cumulative prednisone dose at Week 52.

Safety outcomes were:

- Adverse Event (including infusion-related and hypersensitivity reactions, infections and malignancies) reported throughout the 52-week treatment period and 8 week follow-up.
- Haematological and clinical chemistry parameters (including urinalysis) throughout the 52-week treatment period and 8 week follow-up.
- Vital signs (i.e., pulse rate and systolic and diastolic blood pressure) throughout the 52-week treatment period and 8 week follow-up
- Physical examination
- Suicidality assessment (for subjects ≥12 years of age)
- Immunogenicity during the 52-week treatment period and 8 week follow-up. A 6 month follow-up assessment will be included for all subjects that have a positive anti-belimumab antibody response at the 8 week follow-up assessment.
- Additional safety tests (such as vital signs, physical examinations and laboratory safety tests) or change in timing or addition of assessments may be performed during the course of the study based on newly

available data to ensure appropriate safety monitoring. IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme.

Sample size

As juvenile SLE is an uncommon disease, at the time of protocol development, it was assumed that recruitment of subjects would be challenging. The original decision to enrol 100 subjects was based on feasibility estimations. The following is a description of what statistical information these 100 subjects would have provided. Combining the subject cohorts, a total of 100 subjects would have been randomized. In the first two cohorts, at least 24 subjects would have been randomized in a 5:1 ratio (belimumab:placebo), and the remaining 76 subjects would have been randomized in a 1:1 allocation ratio. Therefore, 58 subjects would have been randomized to belimumab and 42 to placebo. Using the methods of PASS 2005 [Hintze, 2006] for the precision of a confidence interval (CI) around a single proportion; a sample size of 42 would have produced a 95% CI around the sample proportion ± 0.15191 when the estimated proportion of subjects attaining the primary efficacy response at Week 52 is 0.39 (for placebo), and a sample size of 58 would have produced a 95% CI around the sample proportion ± 0.12793 when the estimated proportion is 0.51 (for belimumab).

Sample Size Sensitivity

The estimated proportions cited above are the Week 52 results for placebo and belimumab 10 mg/kg from the combined pivotal Phase 3 studies of IV belimumab in adults with SLE. The estimated proportions of subjects attaining the primary efficacy response at Week 52 from the 76-week Phase 3 study in adults with SLE were 34% and 43% for placebo and belimumab 10 mg/kg, respectively, and for the 52-week study in adults with SLE were 43% and 57%.

Sample size sensitivity calculations were performed considering these results. In this study, for estimated proportions ranging from 0.31 to 0.69, the precision for the 95% CI ranges from approximately 0.12 to 0.13 when the sample size is 58, and from approximately 0.14 to 0.15 when the sample size is 42.

Sample Size Re-estimation

As a consequence of continuing enrolment challenges, despite an increase in the number of participating clinical sites worldwide and concentrated outreach efforts, a sample size reduction based on the extrapolation of recruitment performance to January 2017 was agreed to with the PDCO.

A reduction in subjects from 100 to “at least 70”, although affecting the sample size calculations, did not alter the fact that this study was designed to descriptively evaluate the efficacy and safety of belimumab in Paediatric SLE.

In the first two cohorts, at least 22 subjects were randomized in a 5:1 ratio (belimumab:placebo), and the remaining subjects (at least 48) were randomized in a 1:1 allocation ratio. Therefore, approximately 42 subjects were randomized to belimumab and 28 to placebo. Using the methods of PASS 2005 [Hintze, 2006] for the precision of a CI around a single proportion; a sample size of 28 produces a 95% CI around the sample proportion ±0.18143 when the estimated proportion of subjects attaining the primary efficacy response at Week 52 is 0.39 (for placebo), and a sample size of 42 produces a 95% CI around the sample proportion±0.15286 when the estimated proportion is 0.51 (for belimumab).

Sample size sensitivity calculations were performed considering the primary efficacy response at Week 52 in the pivotal Phase 3 studies of IV belimumab in adults with SLE.

In this study, for estimated proportions ranging from 0.31 to 0.69, the precision for the 95% CI ranges from approximately 0.14 to 0.15 when the sample size is 42 (Belimumab), and from approximately 0.17 to 0.20 when the sample size is 28 (Placebo).

Given the descriptive nature of the study implying that no formal statistical hypothesis testing was planned and also the expected recruitment challenges, the initial target number of 100 subjects is acceptable. When recruitment was found to be even more challenging than expected, a decrease in the target number of subjects from 100 to 70 was proposed and also agreed with PDCO through a modification request to the PIP. The study completion date had by then already been extended by 2 years and the revised sample size implied that recruitment could be completed within a reasonable timeframe.

Randomisation

Subjects were randomised into Part A of BEL114055 in 3 cohorts, with Cohort 3 being stratified by screening SELENA SLEDAI scores (6-12 vs. >13) and by age (5-11 years vs. 12-17 years). Of the randomised subjects, at least 14 subjects were to be younger than 13 years of age and at least 50% were to have a SELENA SLEDAI ≥8 at screening.

Enrolment was staggered to allow PK analysis of the first 2 age cohorts (Cohort 1 in Dec 2015 and Cohort 2 in Jul 2017) to inform the need for adjustment or confirmation of the 10 mg/kg IV belimumab dose. Randomisation and stratification in the 3 cohorts was as follows:

Cohort 1: The first 12 subjects aged 12 to 17 years of age were randomized in a 5:1 ratio to belimumab 10 mg/kg (n=10) or placebo (n=2) on a background of standard of care for 48 weeks. After all subjects in Cohort 1 received at least 8 weeks of treatment, safety review and PK analysis were conducted. Administration of study agent in Cohort 1 subjects continued while safety monitoring and PK analysis were progressed, but no additional subjects were enrolled until the safety review and PK analysis were completed. The 10 mg/kg belimumab dose was confirmed in this age group, and enrollment in Cohort 2 and the older age group (12 to 17 years) of Cohort 3 was initiated.

Cohort 2: At least 10 subjects aged 5 to 11 years of age were planned to be randomised in a 5:1 ratio to belimumab or placebo for 48 weeks on a background of standard of care. After all subjects in Cohort 2 received at least 8 weeks of treatment, safety review and PK analysis were conducted. Administration of study agent in Cohort 2 subjects continued while safety monitoring and PK analysis progressed, but no additional subjects aged 5-11 years were enrolled in the study until the safety review and PK analysis were completed. The 10 mg/kg belimumab dose was confirmed for this age group.

Cohort 3: At least 48 subjects aged 5 to 17 years old were planned to be randomised in a 1:1 ratio to belimumab or placebo on a background of standard of care for 52 weeks. The randomisation of Cohort 3 was stratified by age and SELENA SLEDAI score.

Blinding (masking)

The pharmacist or designee involved in the preparation of the IV infusion of belimumab or placebo was unblinded to the treatment allocation of each subject at that site. The site pharmacist or designee was also the person responsible for receiving, storage, accountability and destruction of unused study agent as well as dispensing study agent, but independent of all other study activities. To prevent unblinding, the injection membrane on the placebo infusion bag was to be punctured with an injection needle.

Once diluted, in a saline bag, belimumab was identical in appearance to placebo and was administered by a blinded member of the site staff.

A designated unblinded GSK Monitor was responsible for oversight of the pharmacist's activities.

All other study site personnel, the subject and the sponsor's blinded study team remained blinded to the investigational product received and to certain biomarkers and pharmacodynamic laboratory results.

Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product was essential for the clinical management or welfare of the subject. GSK Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind treatment codes in the event of a serious adverse event (SAE).

Statistical methods

The study was designed to descriptively evaluate the safety and efficacy of belimumab, and as such no formal statistical hypothesis testing was planned and no p-values were to be presented.

Analysis populations

Intent-to-Treat (ITT)

The analysis of the double-blind treatment phase (Part A) was performed on the ITT population. The ITT population was defined as all subjects who were randomised and treated with at least one dose of study agent in Part A. Summaries using the ITT population grouped subjects according to the treatment that a subject was randomised to receive, regardless of the actual treatment received.

Completers

The Completers population was defined as all subjects who completed all 52 weeks of Part A. A sensitivity analysis was performed on the Completers population.

As-Treated

The as-treated population was defined as all subjects who received at least one dose of study treatment in Part A. Summaries using the as-treated population grouped subjects according to the actual treatment administered to the subject. If a subject received an incorrect treatment, the as-treated analysis was performed according to the treatment that the subject received most of the time (>50% of the time). No sensitivity analysis was done for this population as no subjects received an incorrect dose >50% of the time.

Per-Protocol (PP)

Prior to breaking the blind, data for all subjects in the ITT Population were reviewed to identify protocol violations which could affect the primary endpoint. Subjects with violations with the potential to impact the efficacy analyses were excluded from the PP Population. A sensitivity analysis was not performed for this population as less than 15% of subjects had a violation that could affect the primary endpoint.

Pharmacokinetic (PK)

The PK population comprised all subjects included in the As-Treated population for whom at least one post belimumab treatment PK sample was obtained and analysed. Summaries using this population were based on the actual treatment received if this differed from that to which the subject was randomised.

Primary efficacy endpoint analysis

Subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline were excluded from the analysis.

The number and percentage of subjects achieving an SRI response at Week 52 were presented for belimumab and placebo. A logistic regression model was used to estimate the odds of an SRI response for belimumab vs. placebo. The independent variables in the model included treatment group, baseline age group (5-11 years vs. 12-17 years), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

The SRI response at Week 52 data were summarized by the number and percentage of subjects achieving a response by treatment group, the treatment difference versus placebo, and the odds ratio and 95% CI for belimumab versus placebo. Odds ratio estimates and 95% CI are also displayed for each independent variable in the model.

In support of the primary endpoint, the number and percentage of subjects meeting each of the three components of the primary endpoint at Week 52 was presented.

Analysis of Major Secondary Efficacy Endpoints

The number and percentage of subjects meeting each of 2 definitions of the PRINTO/ACR Juvenile SLE Response Evaluation were analysed using a similar model as described for the primary efficacy endpoint. The 5 endpoints considered in the PRINTO/ACR Juvenile SLE Response Evaluation definition: percent change in ParentGA, percent change in PGA, percent change in SELENA SLEDAI score, percent change in proteinuria, and percent change in PedsQL GC physical functioning domain score were also analysed using ANCOVA or a similar model as described for the primary efficacy endpoint, as appropriate.

In addition, the proportion of subjects with a sustained SRI response (defined as having a response on the primary efficacy endpoint at Weeks 44, 48 and 52) and the proportion of subjects with a sustained ParentGA response (defined as having >0.7 improvement at Weeks 44, 48, and 52 compared to baseline) were analyzed using a similar model as described for the primary efficacy endpoint.

Drop-out/Treatment Failure = Non-responder (DO/TF=NR)

The DO/TF=NR principle was used for all DO/TF efficacy endpoints, including the primary efficacy endpoint and each of the three components of the primary efficacy endpoint. The basic premise of the DO/TF=NR analysis was that a subject who withdraws and does not have a visit within ±28 days of the Day 365 (Week 52) visit, i.e., a dropout, and/or uses a prohibited medication or a non-allowed dose of a restricted medication resulting in treatment failure designation was considered a non-responder in the analysis for Part A.

Additional efficacy analyses

Additional efficacy analyses included e.g. time to first severe SFI flare over the 52 weeks of Part A. Time to first severe flare and time ti first flare (any), respectively was compared between belimumab and placebo using a Cox proportional hazards model, adjusting for baseline age group (5-11 years vs. 12-17 years) and baseline SELENA SLEDAI score (≤12 vs. ≥13).

PK and Safety endpoints

PK and Safety endpoints were summarized using descriptive statistics as appropriate.

An exploratory, post-hoc exposure-response analysis correlating exposure parameters with Week 52 response parameters (analysis included calculation of p-values) was added to assess the impact of exposure variability on the clinical response.

Database locks

There are three database locks planned for this study, corresponding to the primary analysis of Part A, the follow-up analysis of Part B, and the follow-up analysis of Part C. The database was locked for the primary analysis following completion of the double-blind treatment phase (Part A) of the study.

Results

Participant flow

A total of 124 subjects were screened to yield 93 randomised subjects. All 93 randomised subjects received at least 1 dose of study agent. The most common reason for failed screening was physician decision (n=27). The 93 subjects (40 in the placebo group and 53 in the belimumab 10 mg/kg group) in the ITT population were enrolled across 29 sites in 10 countries. Most subjects (81.7%) completed the study through Week 52 (Table 7). The percentage of subjects who withdrew from the study prior to Week 52 was 22.5% in the placebo group and 15.1% in the belimumab group. Adverse event was the most common reason for withdrawal.

Table 7. Subject Completion Status by Week 52 (Part A) (ITT Population)

	Number (%) of Subjects		
	Placebo N=40	Belimumab 10 mg/kg N=53	Total N=93
Completed Week 52 visit	31 (77.5)	45 (84.9)	76 (81.7)
Withdrawn prior to Week 52	9 (22.5)	8 (15.1)	17 (18.3)
Adverse Event	5 (12.5)	3 (5.7)	8 (8.6)
Lack of Efficacy	1 (2.5)	1 (1.9)	2 (2.2)
Physician Decision	0	3 (5.7)	3 (3.2)
Protocol Violation	1 (2.5)	0	1 (1.1)
Withdrawal by Subject	2 (5.0)	1 (1.9)	3 (3.2)

The treatment blind was broken by site personnel for 5 subjects. For 4 subjects (3 placebo, 1 belimumab), this occurred following their early discontinuation from Part A of the study in order that the investigator could best determine their optimal ongoing medical management. For 1 subject (belimumab), the unblinding was a protocol deviation, as the investigator became unblinded to the treatment assignment after inadvertently viewing a report generated by the IXRS to the unblinded site staff. This subject remained in the study and completed Part A.

Recruitment

Subjects were randomised in 3 different cohorts. The first 12 subjects (aged 12-17 ys) were randomised (5:1) into Cohort 1; 10 subjects to the belimumab arm and 2 subjects to placebo. A total of 13 subjects (aged 5-11 ys) were randomised into Cohort 2; 10 subjects to the belimumab arm and 3 subjects to placebo. A total of 68 subjects were randomised (1:1) into Cohort 3; 33 subjects to the belimumab arm and 35 to the placebo arm.

Conduct of the study

The percentage of subjects with important protocol deviations was 43.4% in the belimumab 10 mg/kg group and 32.5% in the placebo group (Table 8).

Table 8. Subjects with Important Protocol Deviations (Part A) (ITT Population)

	Number (%) of Subjects		
	Placebo N=40	Belimumab 10 mg/kg N=53	Total N=93
Any important protocol deviation[a]	13 (32.5)	23 (43.4)	36 (38.7)
Assessments and/or procedures	12 (30.0)	21 (39.6)	33 (35.5)
Not withdrawn after developing withdrawal criteria[b]	2 (5.0)	1 (1.9)	3 (3.2)
Other protocol deviation category	1 (2.5)	0	1 (1.1)
Prohibited medication or device	0	0	0
Received wrong treatment or incorrect dose	0	1 (1.9)	1 (1.1)
Visit, assessment or timepoint window	0	0	0

a. Subjects may be included in more than one category.
b. Post data base lock the study team identified 6 subjects for whom this deviation should have been but were not recorded (3 placebo, 3 belimumab) and 1 subject (placebo) for whom this deviation was incorrectly recorded. Therefore, a total of 8 subjects (4 [10.0%], placebo, 4 [7.5%] belimumab) were not withdrawn after developing withdrawal criteria,

In both treatment groups, the majority of important protocol deviations were in the category of assessments and/or procedures (Table 8). This broad category included deviations related to failure to comply with required collection of PK samples for subjects in Cohorts 1 and 2, failure to comply with required safety and efficacy assessments, failure to comply with requirements for informed consent, failure to comply with procedures for investigational product handling (e.g. incorrect storage or preparation), and failure to maintain the study blind.

In the deviation category of not withdrawn after developing withdrawal criteria, post-data base lock, the study team identified 6 subjects for whom this deviation should have been but were not recorded (3 placebo, 3 belimumab) and 1 subject for whom this deviation was incorrectly recorded (placebo). Therefore, a total of 8 subjects were not withdrawn after developing withdrawal criteria, 4 in the placebo group and 4 in the belimumab group. These subjects who were not promptly withdrawn after receiving prohibited doses of concomitant medications all completed Part A.

No subjects from the placebo group and 1 subject from the belimumab group had an important deviation in the category of wrong treatment or incorrect dose. This deviation occurred at a single study visit at Week 36 when the subject received the wrong treatment (placebo instead of belimumab). This subject had no AEs during the study. At the time of this report, there was one GCP noncompliance issue identified related to a delay in emergency unblinding. The issue was reviewed for root cause and addressed by the Sponsor to ensure future compliance.

There were many protocol deviations in the belimumab group (43.4% important deviations). Important deviations include, but are not limited to, those related to study inclusion or exclusion criteria, adherence to the protocol, conduct of the study, subject management or subject assessment. The CHMP noted that this is a broad category with a mix of compliance with sample collection and protection of blind. Since the extrapolation is mainly based on PK data, this was not further pursued.

Baseline data

Patient demographics are provided in Table 9.

Table 9. Demographics in IV Belimumab Phase 2 Paediatric and Pivotal Phase 3 Adult Studies

	C1056				C1057				BEL114055			
	Placebo N=271	Belimumab N=273	Belimumab		Placebo Belimumab mg/kg N=287	Belimumab 10 mg/kg	1	All N=865	Placebo Belimumab 10	N=40	All N=93	
Sex, n (%)												
Female	252 (91.6)	253 (93.4)	259 (94.9)	764 (93.3)	270 (94.1)	271 (94.1)	280 (96.6)	821 (94.9)	39 (97.5)	49 (92.5)	88 (94.6)	
Race, n (%)												
White/Caucasian	188 (68.4)	192 (70.8)	189 (69.2)	569 (69.5)	82 (28.6)	76 (26.4)	71 (24.5)	229 (26.5)	21 (52.5)	27 (50.9)	48 (51.6)	
Asian	11 (4.0)	6 (2.2)	11 (4.0)	28 (3.4)	105 (36.6)	106 (36.8)	116 (40.0)	327 (37.8)	6 (15.0)	8 (15.1)	14 (15.1)	
Black – African Heritage	39 (14.2)	40 (14.8)	39 (14.3)	118 (14.4)	11 (3.8)	8 (2.8)	11 (3.8)	30 (3.5)	2 (5.0)	3 (5.7)	(5.4)	5
Alaska Native or North/Central/South	36 (13.1)	33 (12.2)	34 (12.5)	103 (12.6)	89 (31.0)	98 (34.0)	92 (31.7)	279 (32.3)	11 (27.5)	15 (28.3)	26 (28.0)	
Native Hawaiian or Islander	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	(0.0)	0
Multiracial	2 (0.7)	3 (1.1)	3 (1.1)	8 (1.0)	1 (0.3)	3 (1.0)	1 (0.3)	5 (0.6)	0 (0.0)	0 (0.0)	(0.0)	0
Hispanic or Latino	55 (20.0)	62 (22.9)	56 (20.5)	173 (21.1)	143 (49.8)	141 (49.0)	136 (46.9)	420 (48.6)	17 (42.5)	26 (49.1)	43 (46.2)	
Age (years), Mean	40.0 (11.9)	40.0 (11.4)	40.5 (11.1)	40.2 (11.5)	36.2 (11.8)	35.0 (10.6)	35.4 (10.8)	35.5 (11.1)	14.8 (2.17)	13.5 (2.59)	14.0 (2.49)	
Age (years), n (%)												
<13									3 (7.5)	18 (34.0)	21 (22.6)	
≥13 - 17									37 (92.5)	35 (66.0)	72 (77.4)	
18 - 45	189 (68.7)	184 (67.9)	178 (65.2)	551 (67.3)	225 (78.4)	236 (81.9)	236 (81.4)	697 (80.6)				
	C1056				C1057				BEL114055			
	Placebo N=271	Belimumab N=273	Belimumab		Placebo Belimumab mg/kg N=287	Belimumab 10 mg/kg	1	All N=865	Placebo	Belimumab 10 mg/kg N=53	All N=40 N=93	
>45 - <65	77 (28.0)	83 (30.6)	92 (33.7)	252 (30.8)	57 (19.9)	48 (16.7)	52 (17.9)	157 (18.2)				
≥65	9 (3.3)	4 (1.5)	3 (1.1)	16 (2.0)	5 (1.7)	4 (1.4)	2 (0.7)	11 (1.3)				

a. A person having origins in any of the original peoples of North and South America (including Central America) and who maintains tribal affiliation or community attachment.

The majority of subjects were female, and the mean age was 14 years. Patients in the belimumab group were more often Hispanic or Latino, but the proportion of African descents were similar in both group. Of note, in the belimumab phase 3 trials, the black population seemed to benefit less from belimumab than the overall population.

Baseline disease activity is shown in **Table 10**.

Table 10. Baseline disease activity

	C1056				C1057				BEL114055		
	Placebo	Belimumab 1 mg/kg	Belimumab 10 mg/kg	All N=819	Placebo	Belimumab 1 mg/kg	Belimumab 10 mg/kg	All N=865	Placebo N=40	Belimumab 10 mg/kg N=93	All
SLE Disease	7.42 (6.72)	7.93 (7.13)	7.20 (7.45)	7.52 (7.10)	5.93 (6.17)	4.96 (4.58)	5.03 (5.07)	5.31 (5.32)	2.66 (1.831)	2.16 (1.993)	2.37 (1.931)
BILAG organ domain at least 1A or 2B	187 (68.0)	173 (63.8)	160 (58.6)	520 (63.5)	166 (57.8)	166 (57.6)	172 (59.3)	504 (58.3)	29 (72.5)	37 (69.8)	66 (71.0)
at least 1A	37 (13.5)	38 (14.0)	24 (8.8)	99 (12.1)	52 (18.1)	58 (20.1)	54 (18.6)	164 (19.0)	6 (15.0)	4 (7.5)	10 (10.8)
SELENA SLEDAI ≤7									6 (15.4)	7 (13.2)	13 (14.1)
≥8									33 (84.6)	46 (86.8)	79 (85.9)
0 - 3	3 (1.1)	5 (1.8)	8 (2.9)	16 (2.0)	1 (0.3)	4 (1.4)	3 (1.0)	8 (0.9)			
4 - 9	131 (47.6)	122 (45.0)	129 (47.3)	382 (46.6)	128 (44.6)	145 (50.3)	127 (43.8)	400 (46.2)			
10 - 11	62 (22.5)	72 (26.6)	65 (23.8)	199 (24.3)	75 (26.1)	53 (18.4)	72 (24.8)	200 (23.1)			
≥12	79 (28.7)	72 (26.6)	71 (26.0)	222 (27.1)	83 (28.9)	86 (29.9)	88 (30.3)	257 (29.7)			
SELENA SLEDAI score Mean (SD)	9.80 (3.97)	9.70 (3.65)	9.52 (3.64)	9.67 (3.75)	9.70 (3.62)	9.56 (3.78)	9.97 (3.88)	9.75 (3.76)	10.4 (3.63)	10.3 (3.34)	10.3 (3.45)
	C1056				C1057				BEL114055		
	Placebo	Belimumab 1 mg/kg	Belimumab 10 mg/kg	All N=819	Placebo	Belimumab 1 mg/kg	Belimumab 10 mg/kg	All N=865	Placebo N=40	Belimumab 10 mg/kg N=53	All N=93
PGA category, n (%) 0 - 1	33 (12.0)	39 (14.4)	51 (18.7)	123 (15.0)	43 (15.0)	38 (13.2)	32 (11.0)	113 (13.1)	9 (22.5)	9 (17.0)	18 (19.4)
>1 - 2.5	239 (86.9)	230 (84.9)	219 (80.2)	688 (84.0)	243 (84.7)	247 (85.8)	256 (88.3)	746 (86.2)	31 (77.5)	44 (83.0)	75 (80.6)
>2.5 - 3	3 (1.1)	2 (0.7)	3 (1.1%	8 (1.0)	1 (0.3)	3 (1.0)	2 (0.7)	6 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
PGA Mean (SD)	1.48 (0.47)	1.44 (0.50)	1.40 (0.54)	1.44 (0.50)	1.42 (0.48)	1.42 (0.47)	1.41 (0.45)	1.42 (0.47)	1.382 (0.4185)	1.341 (0.4264)	1.359 (0.4212)
ParentGA category, n											
0-2.5									9 (22.5)	15 (28.3)	24 (25.8)
>2.5 - 5									15 (37.5)	18 (34.0)	33 (35.5)
>5 - 7.5									14 (35.0)	17 (32.1)	31 (33.3)
>7.5									2 (5.0)	3 (5.7)	5 (5.4)
ParentGA Mean (SD)									4.58 (2.411)	4.26 (2.497)	4.40 (2.452)

SDI/Paediatric SDI Mean (SD)	0.99 (1.45)	1.04 (1.39)	0.94 (1.38)	0.99 (1.41)	0.55 (0.93)	0.60 (1.06)	0.55 (1.00)	0.57 (1.00)	0.2 (0.45)	0.2 (0.56)	0.2 (0.51)
Proteinuria category ≥2	11 (4.0)	7 (2.6)	15 (5.5)	33 (4.0)	21 (7.3)	26 (9.0)	19 (6.6)	66 (7.6)	3 (7.5)	0 (0.0)	3 (3.2)
	C1056				C1057				BEL114055		
	Placebo	Belimumab 1 mg/kg	Belimumab 10 mg/kg	All N=819	Placebo	Belimumab 1 mg/kg	Belimumab 10 mg/kg	All N=865	Placebo N=40	Belimumab 10 mg/kg N=53	All N=93
PGA category, n (%)											
0 - 1	33 (12.0)	39 (14.4)	51 (18.7)	123 (15.0)	43 (15.0)	38 (13.2)	32 (11.0)	113 (13.1)	9 (22.5)	9 (17.0)	18 (19.4)
>1 - 2.5	239 (86.9)	230 (84.9)	219 (80.2)	688 (84.0)	243 (84.7)	247 (85.8)	256 (88.3)	746 (86.2)	31 (77.5)	44 (83.0)	75 (80.6)
>2.5 - 3	3 (1.1)	2 (0.7)	3 (1.1%	8 (1.0)	1 (0.3)	3 (1.0)	2 (0.7)	6 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
PGA Mean (SD)	1.48 (0.47)	1.44 (0.50)	1.40 (0.54)	1.44 (0.50)	1.42 (0.48)	1.42 (0.47)	1.41 (0.45)	1.42 (0.47)	1.382 (0.4185)	1.341 (0.4264)	1.359 (0.4212)
ParentGA category, n											
0-2.5									9 (22.5)	15 (28.3)	24 (25.8)
>2.5 - 5									15 (37.5)	18 (34.0)	33 (35.5)
>5 - 7.5									14 (35.0)	17 (32.1)	31 (33.3)
>7.5									2 (5.0)	3 (5.7)	5 (5.4)
ParentGA Mean (SD)									4.58 (2.411)	4.26 (2.497)	4.40 (2.452)
SDI/Paediatric SDI Mean (SD)	0.99 (1.45)	1.04 (1.39)	0.94 (1.38)	0.99 (1.41)	0.55 (0.93)	0.60 (1.06)	0.55 (1.00)	0.57 (1.00)	0.2 (0.45)	0.2 (0.56)	0.2 (0.51)
Proteinuria category ≥2	11 (4.0)	7 (2.6)	15 (5.5)	33 (4.0)	21 (7.3)	26 (9.0)	19 (6.6)	66 (7.6)	3 (7.5)	0 (0.0)	3 (3.2)
>1 - 2.5	239 (86.9)	230 (84.9)	219 (80.2)	688 (84.0)	243 (84.7)	247 (85.8)	256 (88.3)	746 (86.2)	31 (77.5)	44 (83.0)	75 (80.6)
>2.5 - 3	3 (1.1)	2 (0.7)	3 (1.1%	8 (1.0)	1 (0.3)	3 (1.0)	2 (0.7)	6 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
PGA Mean (SD)	1.48 (0.47)	1.44 (0.50)	1.40 (0.54)	1.44 (0.50)	1.42 (0.48)	1.42 (0.47)	1.41 (0.45)	1.42 (0.47)	1.382 (0.4185)	1.341 (0.4264)	1.359 (0.4212)
ParentGA category, n											
0-2.5									9 (22.5)	15 (28.3)	24 (25.8)
>2.5 - 5									15 (37.5)	18 (34.0)	33 (35.5)
>5 - 7.5									14 (35.0)	17 (32.1)	31 (33.3)
>7.5									2 (5.0)	3 (5.7)	5 (5.4)
ParentGA Mean (SD)									4.58 (2.411)	4.26 (2.497)	4.40 (2.452)
SDI/Paediatric SDI Mean (SD)	0.99 (1.45)	1.04 (1.39)	0.94 (1.38)	0.99 (1.41)	0.55 (0.93)	0.60 (1.06)	0.55 (1.00)	0.57 (1.00)	0.2 (0.45)	0.2 (0.56)	0.2 (0.51)

Proteinuria category ≥2	11	7	15	33	21	26	19	66	3	0	3
Proteinuria level (g/24 Mean (SD)	0.39 (0.81)	0.33 (0.65)	0.40 (0.73)	0.37 (0.74)	0.62 (1.15)	0.63 (1.13)	0.54 (0.91)	0.60 (1.07)	0.5429 (1.12003)	0.2106 (0.24557)	0.3535 (0.77022)

a. For C1056 and C1057, duration is defined as time elapsed between date of SLE diagnosis and the date of informed consent; for BEL114055, duration is defined as treatment start date - SLE diagnosis date + 1.
b. SELENA SLEDAI categories are presented as reported in the respective CSR.
c. The original version of the SDI was used in C1056 and C1057, and the Paediatric SDI was used in BEL114055. The original SDI and the Paediatric SDI are presented together as these are comparable instruments; the Paediatric SDI is based upon the original version of the SDI with additional damage indices unique to the Paediatric population.

Anti-ds-DNA and complement levels are shown in

Table 11.

Table 11. Selected Biomarkers at Baseline in IV Belimumab Phase 2 Paediatric and Pivotal Phase 3 Adult Studies

Biomarker	Number (%) of Subjects										
	C1056				C1057				BEL114055		
	Placebo	Belimumab		All	Placebo	Belimumab		All	lacebo		All
	Belimumab mg/kg	N=275 10 mg/kg	1	N=819	Belimumab mg/kg	N=287 10 mg/kg	1	N=865	Belimumab	N=40 10	N=93
Anti-dsDNA Positive C3/C4[a]	131	125 (46.1)	134 (49.1)	390	156 (53.4)	159 (55.2)	171 (59.0)	486 (56.2)	17 (42.5)	22 (41.5)	39 (41.9)
Anti-dsDNA and/or	265	262 (96.7)	261 (95.6)	788	280 (97.6)	281 (97.6)	284 (97.9)	845 (97.7)	38 (95.0)	52 (98.1)	90 (96.8)
Anti-dsDNA (≥30	174	171 (63.1)	179 (65.6)	524	205 (71.4)	221 (76.7)	218 (75.2)	644 (74.5)	27 (67.5)	38 (71.7)	65 (69.9)
IgG >ULN[c]	108	105 (38.7)	94 (34.4)	307	146 (50.9)	140 (48.6)	151 (52.1)	437 (50.5)	7 (17.5)	15 (28.3)	22 (23.7)
IgA >ULN[c]	38 (13.8)	30 (11.1)	37 (13.6)	105	33 (11.5)	40 (13.9)	36 (12.4)	109 (12.6)	4 (10.0)	7 (13.2)	11 (11.8)
IgM >ULN[c]	4 (1.5)	10 (3.7)	16 (5.9)	30 (3.7)	12 (4.2)	10 (3.5)	9 (3.1)	31 (3.6)	3 (7.5)	1 (1.9)	4 (4.3)
C3 Low[d]	116	100 (36.9)	115 (42.1)	331	132 (46.0)	148 (51.4)	147 (50.7)	427 (49.4)	12 (30.0)	20 (37.7)	32 (34.4)
C4 Low[d]	143	141 (52.0)	147 (53.8)	431	160 (55.7)	173 (60.1)	180 (62.1)	513 (59.3)	15 (37.5)	21 (39.6)	36 (38.7)
BLyS Above LOQ (≥0.5 ng/mL)	268/271 (98.9)	267/270 (98.9)	263/268 (98.1)	798/809 (98.6)	273/283 (96.5)	273/285 (95.8)	281/285 (98.6)	827/853 (97.0)	40/40 (100.0)	50/50 (100.0)	90/90 (100.0)

Note: For parameters where all subjects were assessed data are shown as number of subjects meeting the criterion (percent of subjects meeting criterion using the N as the denominator). For parameters where number of subjects assessed differs from N data are shown as number of subjects meeting the criterion/number of subjects assessed (percent of subjects meeting criterion where number assessed is the denominator).

a. Anti-dsDNA positive (≥30 IU/mL) and Low Complement (C3 <90 mg/dL or C4 <10 mg/dL).
b. ANA positive (≥80 titer); Anti-dsDNA positive (≥30 IU/mL).
c. C1056 and C1057: IgG ULN=16.18 g/L; IgA ULN=4.63 g/L; IgM ULN=2.71 g/L.
d. C1056 and C1057: C3 low=<900 mg/L, C4 low=<16 mg/dL; BEL114055: C3 low=<90 mg/dL, C4 low=<10 mg/dL

More subjects in the belimumab group were anti-ds-DNA positive and had low complement levels, indicating high disease activity, but the differences are small.

Numbers analysed

Analysis populations are summarized in Table 12. All 93 randomized subjects were included in the ITT population.

Table 12. Number of Subjects in Analysis Populations

	Placebo	Belimumab 10 mg/kg	Total
Randomized	40	53	93
Population			
Intent-to-Treat[a]	40	53	93
Per Protocol[b]	39	52	91
Completers	31	45	76
As-Treated	40	53	93
PK	0	53	53

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 Intent-to-Treat Population and had no important protocol deviations that could affect the primary endpoint. A sensitivity analysis was not performed for this population as less than 15% of subjects had a violation that could affect the primary endpoint.

All randomised subjects received at least one dose of study treatment, and is therefore identical to the ITT population. As stated in the RAP, the PP population was to be used only for a sensitivity analysis of the primary efficacy endpoint if more than 15% of subjects had a violation that could affect the primary efficacy endpoint. One subject in each group was excluded from PP analysis because of important protocol deviations; hence no analysis based on the PP population was performed. A sensitivity analysis of the primary endpoint, SRI response at Week 52, was however performed based on the Completers analysis population. Overall, a higher proportion of the subjects in the belimumab arm than in the placebo arm completed the study: 45/53 (84.9%) and 31/40 (77.5%) respectively.

Prior and concomitant medications

Baseline medication is shown in Table 13.

Table 13. Selected SLE Medication Use at Baseline in IV Belimumab Phase 2 Paediatric and Pivotal Phase 3 Adult Studies

	C1056				C1057				BEL114055		
SLE Medication	Placebo N=275	Belimumab 1 mg/kg N=271	Belimumab 10 mg/kg N=273	All N=819	Placebo N=287	Belimumab 1 mg/kg N=288	Belimumab 10 mg/kg N=290	All N=865	Placebo N=40	Belimumab 10 mg/kg N=53	All N=93
Total steroid use, n (%)	212 (77.1)	211 (77.9)	200 (73.3)	623 (76.1)	276 (96.2)	276 (95.8)	278 (95.9)	830 (96.0)	38 (95.0)	50 (94.3)	88 (94.6)
Average daily prednisone dose (mg/day), mean (SD)[a]	9.4 (8.9)	8.7 (7.6)	8.4 (7.9)	8.8 (8.2)	11.9 (7.9)	12.9 (8.6)	13.2 (9.5)	12.7 (8.7)	12.20 (8.709)	9.11 (5.580)	10.44 (7.218)
Anti-malarials, n (%)	180 (65.5)	171 (63.1)	168 (61.5)	519 (63.4)	201 (70.0)	195 (67.7)	185 (63.8)	581 (67.2)	31 (77.5)	44 (83.0)	75 (80.6)
Immunosuppressants, n (%)	154 (56.0)	153 (56.5)	148 (54.2)	455 (55.6)	122 (42.5)	120 (41.7)	123 (42.4)	365 (42.2)	27 (67.5)	33 (62.3)	60 (64.5)
NSAIDs, n (%)	119 (43.3)	114 (42.1)	101 (37.0)	334 (40.8)	59 (20.6)	56 (19.4)	58 (20.0)	173 (20.0)	12 (30.0)	11 (20.8)	23 (24.7)

Source: CRD-adult T22; CSR BEL114055 Table 1.28
a. Steroids were converted to prednisone equivalent.

Outcomes and estimation

Primary efficacy endpoint – SRI response at Week 52

Table 14. SRI Response at Week 52 for IV Belimumab Phase 2 Paediatric and Pivotal Phase 3 Adult Studies (DO/TF=NR)

	C1056			C1057			BEL114055	
	Placebo N=275 N=271	Belimumab 1 mg/kg	Belimumab 10 mg/kg N=273	Placebo N=287 N=288	Belimumab 1 mg/kg	Belimumab 10 mg/kg N=290	Placebo N=40 N=53	Belimumab 10 mg/kg
Response, n (%)	93 (33.8)	110 (40.6)	118 (43.2)	125 (43.6)	148 (51.4)	167 (57.6)	17 (43.6)[a]	28 (52.8)
Observed difference vs. placebo (%)	-	6.77	9.41	-	7.83	14.03	-	9.24
Odds ratio (95% CI)[b] vs. placebo	-	1.34 (0.94, 1.91)	1.52 (1.07, 2.15)	1.55 -	(1.10, 2.19)	1.83 (1.30, 2.59)	-	1.49 (0.64, 3.46)

a. One ITT subject did not have a baseline SELENA SLEDAI assessment and, therefore, did not contribute to SRI/component analyses.

b. For C1056 and C1057, Odds ratio (95% CI) is from logistic regression for the comparison between each belimumab dose and placebo with covariates. For individual studies, covariates include baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline proteinuria level (<2 g/24 hour vs. ≥2 g/24 hour equivalent) and race (African descent or indigenous−American descent vs. Other).

For BEL114055, Odds ratio (95% CI) is from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

Key Supportive and Sensitivity Analyses of the Primary SRI Efficacy Endpoint

Included in the pre-specified sensitivity analyses in BEL114055 was SRI6 response at Week 52 (Table 15). The SRI6 was defined identically to the SRI except the SRI6 used a higher threshold of improvement for SELENA SLEDAI, a ≥6 point reduction, in order for a subject to be declared a responder. Within BEL114055, SRI6 results were consistent with the primary efficacy endpoint analysis. The odds of being a SRI6 responder at Week 52 was greater for Paediatric subjects in the belimumab group compared with the placebo group, which is consistent with the corresponding results in the 2 pivotal Phase 3 adult studies.

Table 15. SRI6 Response at Week 52 (sensitivity analysis) in IV Belimumab Phase 2 Paediatric and Pivotal Phase 3 Adult Studies

	C1056			C1057			BEL114055	
	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	Placebo N=40	Belimumab 10 mg/kg N=53
SRI6 using SELENA SLEDAI ≥6 point reduction								
Week 52[b]	52 (18.9)	78 (28.8)	84 (30.8)	81 (28.2)	106 (36.8)	127 (43.8)	13/38 (34.2)[a]	21/51 (41.2)
Odds ratio (95% CI) vs. placebo[c]	-	1.77 (1.17, 2.68)	2.00 (1.33, 3.01)	-	1.82 (1.25, 2.67)	2.20 (1.51, 3.20)	-	1.35 (0.56, 3.22)

a. One ITT subject did not have a baseline SELENA SLEDAI assessment and, therefore, did not contribute to SRI/component analyses.
b. Premature withdrawal and missing data were handled as described in Section 1.3.4.6.6.
c. For C1056 and C1057, Odds ratio (95% CI) is from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤9 vs. ≥10), baseline proteinuria level (<2 g/24 hour vs. ≥2 g/24 hour equivalent) and race (African descent or indigenous−American descent vs. other). For BEL114055, Odds ratio (95% CI) is from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

Supplemental analysis (RAP addendum)

Supplemental analyses were performed based on regulatory agency feedback. Below are results for the SRI response and its 3 components at Week 52 are presented by baseline age (5-11 years [Cohort 2] and 12-17 years [Cohorts 1 + 3]) and Cohort 3 alone (Table 16).

Table 16. SRI Response and Components of SRI Response at Week 52 by Baseline Age and Cohort 3

	Baseline Age 5-11 Years (Cohort 2)		Baseline Age 12-17 Years (Cohort 1+3)		Cohort 3	
	Placebo N=3	Belimumab 10 mg/kg N=10	Placebo N=37	Belimumab 10 mg/kg N=43	Placebo N=35	Belimumab 10 mg/kg N=33
SRI Response[a], n/n (%)	1/3 (33.3)	5/10 (50.0)	16/36 (44.4)	23/43 (53.5)	14/34 (41.2)	15/33 (45.5)
Observed difference vs. placebo	-	16.67	-	9.04	-	4.28
Odds ratio (95% CI)[b] vs. placebo	-	2.00 (0.13, 29.80)	-	1.44 (0.59, 3.50)	-	1.19 (0.45, 3.13)
4-point reduction in SELENA SLEDAI[a], n/n (%)	1/3 (33.3)	5/10 (50.0)	16/36 (44.4)	24/43 (55.8)	14/34 (41.2)	16/33 (48.5)
Observed difference vs. placebo	-	16.67	-	11.37	-	7.31
Odds ratio (95% CI)[b] vs. placebo	-	2.00 (0.13, 29.80)	-	1.58 (0.65, 3.85)	-	1.34 (0.51, 3.53)
No worsening in PGA[a], n/n (%)	1/3 (33.3)	8/10 (80.0)	25/36 (69.4)	32/43 (74.4)	23/34 (67.6)	23/33 (69.7)
Observed difference vs. placebo	-	46.67	-	4.97		2.05
Odds ratio (95% CI)[b] vs. placebo	-	8.00 (0.46, 139.29)	-	1.28 (0.48, 3.43)		1.10 (0.39, 3.09)
No new 1A/2B BILAG domain scores[a], n/n (%)	1/3 (33.3)	7/10 (70.0)	23/36 (63.9)	32/43 (74.4)	21/34 (61.8)	24/33 (72.7)
Observed difference vs. placebo	-	36.67		10.53		10.96
Odds ratio (95% CI)[b] vs. placebo	-	4.67 (0.30, 73.36)		1.64 (0.63, 4.32)		1.65 (0.59, 4.63)

a. One ITT subject did not have a baseline SELENA SLEDAI assessment and, therefore, did not contribute to SRI/component analyses.
b. Odds Ratio (95% confidence interval) is from a logistic regression model for the comparison between belimumab and placebo without adjustment for any covariates.

Major secondary endpoints

A summary of the major secondary endpoints is presented in Table 17.

Table 17. Major Secondary Endpoints in IV Belimumab Phase 2 Paediatric Study

	lacebo N=40	nab 10 mg/kg N=53
Percent of subjects meeting PRINTO/ACR Juvenile SLE Response Definition 1[a] at Week 52 (DO/TF=NR) Response, n/n (%)	14/40 (35.0)	32/53 (60.4)
Observed difference vs. Placebo	-	25.38
Odds ratio (95% CI)[b] vs. placebo	-	2.74 (1.15, 6.54)
Percent of subjects meeting PRINTO/ACR Juvenile SLE Response Definition 2[c] at Week 52 (DO/TF=NR) Response, n/n (%)	11/40 (27.5)	28/53 (52.8)
Observed difference vs. Placebo	-	25.33
Odds ratio (95% CI)[b] vs. placebo		2.92 (1.19, 7.17)
Percent change in ParentGA at Week 52 (LOCF)[d]		
N	38	47
Mean (±SE)	2.86±19.016	-19.40±21.561
Percent change in PGA at Week 52 (LOCF)[d]		
N	40	53
Mean (±SE)	-48.802±6.6475	-56.525±6.0156
	lacebo N=40	nab 10 mg/kg N=53
Percent change in SELENA SLEDAI at Week 52 (LOCF)[d]		
N	39	53
Mean (±SE)	-38.0±6.33	-43.3±6.01
Percent change in PedsQL Physical Functioning Domain Score at Week 52 (LOCF)[d]	40	53
N		
Median (Min, Max)	12.5 (-53, 575)	10.5 (-100, 280)

Percent Change in 24-hour Proteinuria at Week 52 (LOCF)[e]		
N	40	53
Median (Min, Max)	7.0920 (-90.568, 570.149)	-2.1277 (-85.073, 1681.884)
Proportion of subjects with a sustained SRI response (DO/TF=NR)[f]	16/39 (41.0)	23/53 (43.4)
Response, n/n (%)		
Observed difference vs. Placebo	-	2.37
Odds ratio (95% CI)[b] vs. Placebo	-	1.08 (0.46, 2.52)
Proportion of subjects with a sustained ParentGA response (DO/TF=NR)[g]	12/36 (33.3)	26/44 (59.1)
Response, n/n (%)		
Observed difference vs. Placebo	-	25.76
Odds ratio (95% CI)[h] vs. Placebo	-	3.49 (1.23, 9.91)

a. 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.
b. Odds ratio (95% confidence interval) is from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).
c. 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.
d. Subjects with a baseline score of zero are excluded from the analysis due to division by zero.
e. Subjects with a baseline proteinuria of zero are excluded from the analysis due to division by zero.
f. Sustained SRI response from Week 44 through Week 52.
g. A sustained ParentGA is defined as >0.7 improvement from baseline in ParentGA at Weeks 44, 48, and 52.
h. Odds ratio (95% confidence interval) is from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline ParentGA score, baseline age (5-11 vs. 12-17), and baseline SELENA SLEDAI score (≤12 vs. ≥13).

Additional efficacy analyses

Prednisone

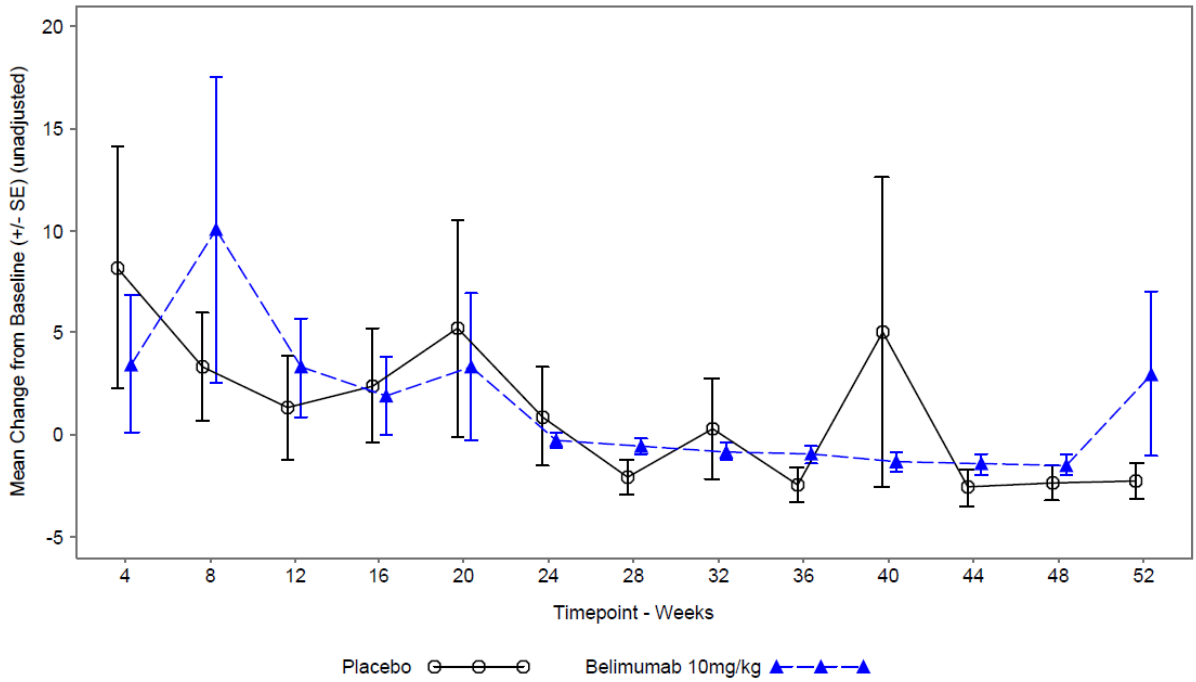
The following analyses for prednisone were performed:

- Percent of subjects whose average prednisone dose has been reduced by ≥25% from baseline during Week 44 to Week 52 (DO/TF=NR).
- Mean absolute changes from baseline in average daily prednisone equivalent dose (mg/kg) by visit (observed).
- Percent of subjects with any decrease in daily prednisone equivalent dose by visit (DO/TF=NR).
- Percent of subjects with any increase in daily prednisone equivalent dose by visit (LOCF).
- Cumulative prednisone dose at Week 52.

The percentage of subjects who achieved ≥25% reduction in daily prednisone equivalent dose from baseline during Week 44 to Week 52 was 21.1% for the placebo group and 20.0% for the belimumab 10 mg/kg group (Odds Ratio: 0.92, 95% CI: 0.29, 2.88).

For the analysis of prednisone dose change from baseline, there were no notable differences between the placebo and belimumab 10 mg/kg groups (Figure 13). At Week 52, the placebo group had an adjusted mean (SE) decrease in prednisone dose from baseline of 6.126 (5.8251) mg/day, while the belimumab group had an adjusted mean decrease of 1.063 (4.6262) mg/day.

Figure 13. Prednisone Change from Baseline by Visit (Observed) (Part A)



The percentage of subjects with any decrease in prednisone at Week 52 was 23.7% in the placebo group and 26.0% in the belimumab group (Odds Ratio: 1.26; 95% CI: 0.43, 3.63).

The percentage of subjects with any increase in prednisone at Week 52 was 15.0% in the placebo group and 13.2% in the belimumab group (Odds Ratio: 0.85; 95% CI: 0.25, 2.96).

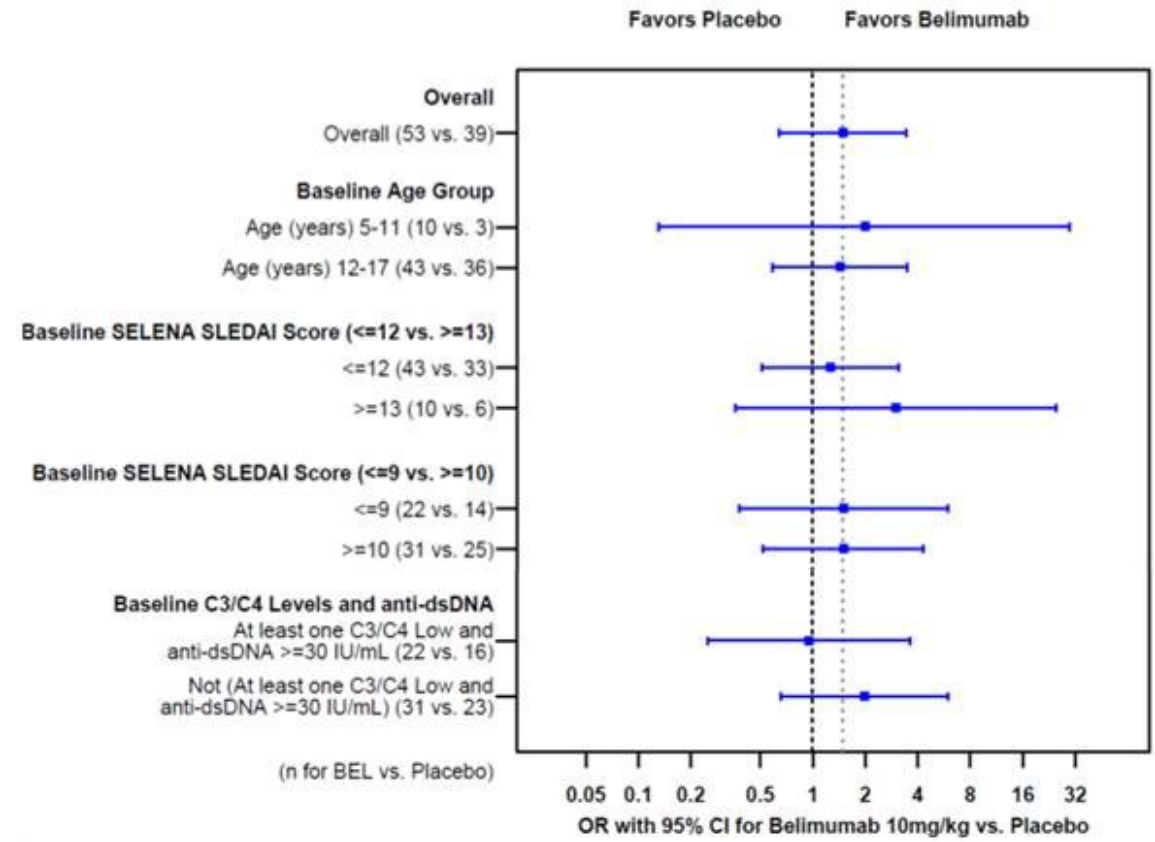
The mean (SD) cumulative prednisone dose over 52 weeks was 4999.4 (10400.61) mg in the belimumab 10 mg/kg group and 6882.7 (10024.16) mg in the placebo group.

Comparison of Results in Sub-Populations

To understand the efficacy of IV belimumab in different Paediatric patient subpopulations, evaluation of the primary endpoint, SRI response at Week 52, was performed in subgroups in BEL114055 based on age, baseline SELENA SLEDAI score (≤12 vs. ≥13; ≤9 vs. ≥10; ≤7 vs. ≥8), and baseline disease activity. For subgroups based on age and SELENA SLEDAI score, the results were consistent with pooled data from the pivotal Phase 3 adult studies, with the observed difference between treatment groups and odds ratios vs. placebo favoring belimumab 10 mg/kg (In BEL114055, there was no statistically significant difference in SRI response rates between treatment groups in the subgroup of 38 subjects with positive anti-dsDNA and low C3 and/or C4 indicating high disease activity (target population according to current indication). In fact, the SRI response rate in this subpopulation was numerically lower for belimumab. This result is in contrast to that observed in the pivotal Phase 3 adult studies, which is possibly related to the small number of subjects in the subgroups in BEL114055.

Figure 14). In BEL114055, there was no statistically significant difference in SRI response rates between treatment groups in the subgroup of 38 subjects with positive anti-dsDNA and low C3 and/or C4 indicating high disease activity (target population according to current indication). In fact, the SRI response rate in this subpopulation was numerically lower for belimumab. This result is in contrast to that observed in the pivotal Phase 3 adult studies, which is possibly related to the small number of subjects in the subgroups in BEL114055.

Figure 14. Odds Ratio Plot of Primary SRI Response at Week 52 by Subgroup in IV Belimumab Phase 2 Paediatric Study



Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18. Summary of Efficacy for trial BEL114055

Title: A Multi-center, 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 Paediatric Patients with Systemic Lupus Erythematosus (SLE) – Double-Blind Endpoint Analysis (Part A)		
Study identifier	BEL114055	
Design	Multicenter, Randomised, Double-blind, Placebo-controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 Weeks N/A Ongoing (up to 10 years)
Hypothesis	The study was designed to descriptively evaluate the safety and efficacy of belimumab, and no formal statistical hypothesis testing was planned.	
Treatments groups	Belimumab	Belimumab 10 mg/kg body weight administered by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48 (n=53).
	Placebo	Placebo administered by IV infusion on Days 0, 14, 28 and then every 28 days through Week 48 (n=40).

Endpoints and definitions	Primary endpoint	SRI4 Response at Week 52	≥4 point reduction from baseline in SELENA SLEDAI score and no worsening in PGA and no new BILAG 1A/2B)
	Secondary endpoint	PRINTO/ ACR Juvenile SLE Response Evaluation Criteria for Improvement in SLE at Week 52	Proportion of subjects with at least 50% improvement in any 2 of 5 endpoints (percent change in ParentGA, PGA, SELENA SLEDAI score, 24-hour proteinuria, and PedsQL GC physical functioning domain score at Week 52) and no more than 1 of the remaining worsening by more than 30%
	Secondary endpoint	Percent change in ParentGA at Week 52	The patient's overall well-being at the moment rated on a 21-numbered circle visual analog scale.
	Secondary endpoint	Percent change in PGA at Week 52	VAS scale for the physician to indicate the subject's overall disease activity at a particular visit.
Database lock	Part A: 24 January 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, Week 52		
Descriptive statistics and estimate variability	Treatment group	Belimumab	Placebo
	Number of subject	53	40
	SRI4 Response, n (%)	28 (52.8)	17 (43.6)
	Observed difference vs. placebo	9.24	
	Odds ratio (95% CI) vs. placebo	1.49 (0.64, 3.46)	
Analysis description	**Secondary analysis**		
Descriptive statistics and estimate variability	PRINTO/ ACR Juvenile SLE Response Evaluation Criteria for Improvement in SLE at Week 52, n (%)	32 (60.4)	14 (35.0)
	Observed difference vs. placebo	25.38	
	Odds ratio (95% CI) vs. placebo	2.74 (1.15, 6.54)	
	ParentGA Percent Change from Baseline at Week 52, Mean ± SE	-19.40 ± 21.561	2.86 ± 19.016
	Percent Change in PGA at Week 52, Mean ± SE	-56.525 ± 6.0156	-48.802 ± 6.6475

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The IV belimumab Paediatric study agreed in the PIP, BEL114055, consists of three phases. The study enrolled 93 subjects randomised to treatment with belimumab or placebo. Eligible subjects for the study was 5 to 17 years of age and had clinically active SLE disease, defined as a SELENA SLEDAI disease activity score of ≥6 at screening. Subjects had to have 4 or more of the 11 American College of Rheumatology (ACR) criteria for the classification of SLE either at screening or in the past. Subjects also had to have positive test result for anti-nuclear antibody (ANA) titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL serum antibody.

Patients who had severe active lupus nephritis, severe active CNS lupus, primary immunodeficiency, IgA deficiency or acute or chronic infections requiring management were excluded from the study.

There are no important differences between the eligibility criteria in BEL114055 and the phase III studies in adults.

Subjects were randomised into 3 cohorts. The first subjects aged 12-17 years were randomized in a 5:1 ratio to belimumab or placebo (cohort 1). The first subjects aged 5-11 years were also randomised in a 5:1 ratio to belimumab or placebo (cohort 2). After all subjects in cohort 1 and 2 received at least 8 weeks of treatment, safety review and PK analysis were conducted. Thereafter, the rest of the subjects were randomised in a 1:1 ratio to belimumab or placebo. All subjects received stable background immunosuppressive treatment. The double-blind period was 52 weeks, and was followed by an open-label extension.

The primary efficacy endpoint was SRI4 response at week 52. SRI4 is defined as: ≥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 at the time of assessment (i.e., at Week 52). The study was only powered for descriptive efficacy.

The primary efficacy endpoint was identical to the adult intravenous trials.

The approach to use staggered enrolment and randomisation into different cohorts to be able to conduct PK and safety analyses and, if found necessary, to adjust the dose before continued recruitment to initially Cohort 2 and eventually also Cohort 3 was endorsed by the CHMP. The GSK Safety Review Team (SRT) was to review available blinded safety, key biomarker and PK data and a recommendation by consensus was to be made regarding dose confirmation or adjustment and the initiation of the subsequent cohorts. The PK analysis and recommendation regarding dose confirmation or adjustment was also to be reviewed by the IDMC. The PK interim data reviews and IDMC safety data reviews were hence pre-planned and have been thoroughly described by the MAH.

At the Cohort 1 review based on data from the first 12 randomised subjects aged 12-17 years, the 10 mg/kg belimumab dose was confirmed. Based on the review of Cohort 2 data, at least 10 subjects aged 5-11 years, it was concluded that the 10 mg/kg belimumab dose was appropriate also for this age group.

The procedures used to achieve and maintain blinding were considered sufficient by the CHMP.

This was a safety, tolerability, PK and efficacy evaluation study. A primary efficacy endpoint and a number of secondary efficacy endpoints were pre-defined but efficacy as well as safety was to be analysed descriptively. No formal efficacy hypothesis testing was planned and the sample size was primarily based on feasibility. Overall, the analyses as planned and performed were considered acceptable by the CHMP.

In case of drop-outs or treatment failures, the use of a non-responder imputation was supported by the CHMP. In the primary efficacy analysis, subjects with baseline SELENA SLEDAI score less than 4 or missing SRI components at baseline were to be excluded from the analysis. In the end, one ITT subject in the placebo arm who did not have a baseline SELENA SLEDAI assessment was excluded and, therefore, did not contribute to SRI/component analyses. Regarding the definition of the ITT population, all randomised subjects received at least one dose; hence ITT analyses comprised all randomised subjects. In addition, sensitivity analyses were planned and have been performed.

Efficacy data and additional analyses

A total of 93 subjects were included, and all received at least 1 dose of study agent (ITT population).

The study was conducted in the US, South America, Europe, and Asia. The majority of subjects were female (94.6%), and the mean age was 14 years (range 6 to 17 years). Patient median age was 15 years (range 6 to 17 years). In the 5- to 11-year-old-group (n=13) the SELENA-SLEDAI score ranged from 4 to 13, and in 12- to 17-year-old-group (n=79) the SELENA-SLEDAI score ranged from 4 to 20. Patients in the belimumab group were more often Hispanic or Latino; the proportion of African descent was similar in both groups.

Subjects in the placebo group had a slightly longer disease duration and a more severe disease defined by BILAG score. These BILAG A items were mainly mucocutaneous (n=3 in each group) and musculoskeletal (n=2 in the placebo group). In each group, there was one subject with renal BILAG domain A. Disease activity as per SLEDAI score was balanced in both groups. Subjects in the placebo group had more proteinuria, both in mean and with more subjects with higher proteinuria categories. Also, more subjects in the belimumab group were anti-ds-DNA positive and had low complement levels, indicating high disease activity, but the differences are small and not likely to impact the study result.

The majority of patients were on steroids and antimalarials. The proportion of subjects with other immunosuppressants was slightly higher in the placebo group, which could indicate a more severe disease.

The study was not powered for any formal comparisons between randomised treatments. The primary efficacy endpoint, SRI4 response at week 52, was achieved by 28/53 subjects (52.8%) in the belimumab group and 17/40 subjects (43.6%) in the placebo group. The difference was not statistically significant, but numerically the response rate was similar to the response rate in the phase 3 studies in adults (43.2% in belimumab vs 33.8% in placebo in C1056 and 57.6% in belimumab vs 43.6% in placebo in C1057). Also for SRI6, the response rate was numerically higher in the belimumab group vs placebo, although the differences were smaller than compared to the phase 3 trials in adults.

The proportion of subjects meeting the PRINTO/ACR Juvenile SLE response definition was 32/53 subjects (60.4%) in the belimumab group and 14/40 (35.0%) in the placebo group. The proportion of subjects with PRINTO/ACR response was higher in the belimumab group compared to placebo, regardless if 50% or 30% improvement was used in the definition.

The percent change in parentGA from baseline was numerically higher in the belimumab group. No big difference was noted in percent change in PGA from baseline. The percent change in proteinuria increased in the placebo group and decreased in the belimumab group. This is an interesting finding, but the changes are small and it must be recalled that there were more subjects in the placebo group with baseline proteinuria possibly indicating a higher proportion of subjects with baseline nephritis. Therefore, the CHMP couldn't draw any conclusion on this finding.

With regards to prednisone levels, the percentage of subjects who achieved ≥25% reduction in prednisone dose from baseline during Week 44 to Week 52 was numerically lower for belimumab than for placebo.

Also for mean absolute changes from baseline in average daily prednisone equivalent dose, the results were in favour of placebo. The percentage of subjects with any decrease from baseline in prednisone dose over 52 weeks was numerically higher for the belimumab group. Also, the mean cumulative prednisone dose was lower in the belimumab group. The higher baseline prednisone levels in the placebo group (mean 12.20 mg/day) than in the belimumab group (mean 9.11 mg/day) however limits the value of this finding. The CHMP concluded that it could not be considered that belimumab has a steroid-sparing effect in children.

When comparing the primary efficacy endpoint in different subpopulations (age group, baseline SELENA SLEDAI score, baseline C3/C4 levels and anti-dsDNA), there was no clear difference in SRI response rates between treatment groups in the subgroup of 38 subjects (22 Benlysta and 16 placebo) with positive anti-dsDNA and low C3 and/or C4, which is the proposed target population for belimumab treatment. The results for subjects with positive anti-dsDNA and low C3 and/or C4 are somewhat surprising since these subjects responded best to belimumab in the studies in adult SLE, which led to the currently approved indication. In fact, the SRI response rate in the subpopulation of subjects with high disease activity defined as low complement C3/C4 levels or high anti-ds-DNA levels (target population according to current indication) was numerically lower for belimumab (8/22 subjects, 36.4%) than for placebo (6/16 subjects, 37.5%). However, it was recognised that the small study size does not allow any conclusions to be drawn from the subgroup analyses. Indeed, the study was not powered for any formal comparisons between randomised treatments.

Prepubertal onset of SLE is uncommon, and more often associated to rare monogenic variants which sometimes lead to severe forms of the disease. Compared with individuals with disease onset during adulthood, young children with SLE have more commonly multiorgan disease, acute disease onset and ongoing active inflammation over time (Brunner et al, Ann Rheum Dis 2018;0:1–9). In study BEL114055, only 13 subjects were aged 5-11 years out of which 10 were treated with Benlysta. The characteristics of these children were similar to the adults included in the studies from which efficacy is to be extrapolated and the magnitude of the effect was also similar. Although data are limited, there were no important differences in disease characteristics between children and adults, nor between children aged 5-11 and older children aged ≥12 years. Therefore, the CHMP considered that the data can be extrapolated also in the younger population.

2.4.4. Conclusions on the clinical efficacy

The rarity of the disease and the accompanying difficulties of recruiting patients to an adequately powered phase 3 study in paediatric SLE patients were acknowledged by the CHMP. The current study was not powered for a statistical comparison of superiority of belimumab vs placebo, and the assessment is primarily based on PK data and descriptive clinical data.

The clinical outcome of the paediatric study is compared to the outcome from the phase 3 studies in adults with an equal design. There was a numerically higher response rate for the primary and most of the secondary endpoints for belimumab than for placebo. In the subjects aged 5-11 years included in the study, there were no important differences in disease characteristics between children and adults, nor between children aged 5-11 and older children aged ≥12 years.

In conclusion, the clinical data allows for an extrapolation based on PK data. The differences between the groups are largely comparable to the differences observed in the phase 3 studies in adults, supporting an indication in paediatric patients aged 5 years and above.

2.5. Clinical safety

Introduction

The safety of belimumab in patients with SLE has been evaluated in 3 placebo-controlled intravenous studies and 1 placebo-controlled subcutaneous study, including a total of 674 patients with SLE exposed to the approved dose of 10 mg/kg IV (out of which 472 were exposed for at least 52 weeks), and 556 patients exposed to 200 mg Benlysta subcutaneously once weekly for up to 52 weeks.

The majority of patients were also receiving one or more of the following concomitant treatments for SLE: corticosteroids, immunomodulatory medicinal products, anti-malarials, non-steroidal anti-inflammatory medicinal products.

As presented in the SmPC, where also post-marketing reports are included, adverse reactions were reported in 87% of Benlysta-treated patients and 90% of placebo-treated patients. The most frequently reported adverse reactions (≥5% of patients with SLE treated with Benlysta plus standard of care and at a rate ≥1% greater than placebo) were viral upper respiratory tract infections, bronchitis, and diarrhoea. The proportion of patients who discontinued treatment due to adverse reactions was 7% for Benlysta-treated patients and 8% for placebo-treated patients.

Methods

Safety assessments for this study were the monitoring of AEs, clinical laboratory tests (Protocol Appendix 5), vital signs (systolic and diastolic blood pressure [sitting], heart rate, and body temperature), physical examinations, and immunogenicity. Adverse events of special interest (AESI) were malignant neoplasms, infusion/anaphylaxis/hypersensitivity reactions, all infections of special interest, depression/suicide/self-injury, and deaths. Subjects 12 years and older were assessed for suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS; see Protocol Section 6.3.9). Children less than 12 years of age were not assessed with the C-SSRS as the C-SSRS has not been fully validated for use in children less than 12 years of age.

The investigator or site staff were responsible for detecting, documenting and reporting events that met the definition of an AE or SAE. AE information volunteered by the subject, discovered by investigator questioning or detected by other means was collected from the start of study treatment until the follow-up contact. The following information on AEs was obtained:

- Duration (start and stop dates).
- Severity (mild, moderate, severe).
- Causality (reasonable possibility yes/no).
- Actions taken and outcome.

SAEs were to be collected over the same time period as for AEs. However, SAEs assessed as related to study participation (e.g., investigational product, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, and all AEs of special interest (including serious and non-serious events) were to be recorded from the time a subject consented to participate in the study up to and including any follow-up contact.

Any abnormal laboratory test result or other safety assessment (e.g., ECGs, radiological scans, vital signs measurements), including those that worsened from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator was to be recorded as an AE or SAE, as appropriate per definition.

The CHMP noted that there are different definitions for severe adverse events and serious adverse events.

Adverse events were classified according to severity:

Grade 1- Mild - causing no limitation of usual activities (Grade 1 DMID).

Grade 2- Moderate - causing some limitation of usual activities (Grade 2 DMID)

Grade 3- Severe - causing inability to carry out usual activities (Grade 3 or 4 DMID). An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE.

Serious adverse event (SAE) is defined as follows:

a. Results in death

b. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin

≥2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

Immunogenicity

For the immunogenicity assessment, a tiered testing approach was used. Samples were first screened for the presence of anti-belimumab antibodies (anti-drug antibodies [ADA]). Samples with a screening result above the screening cut-point of the assay were then tested to confirm specificity. If specificity was confirmed, samples were then tested for the presence of neutralizing antibodies as well as assigning a relative titre for the ADA response.

Briefly, for the binding assay, there were 3 testing steps. A screening assessment was performed which produces a result of positive or negative. For samples with a positive screening result, a confirmation assay was then carried out, which also produces a result of positive or negative. For samples with a positive confirmation result, a titre value was determined. Subjects confirmed positive in the binding assay were also further tested for the presence of neutralizing antibodies. Neutralization assay results are also reported as positive or negative.

Patient exposure

As of 08 March 2018, Belimumab has been investigated in approximately 33 completed or ongoing Phase 1, 2, and 3 clinical studies conducted by GlaxoSmithKline (GSK). An estimated 6,841 subjects (13,690 patient years) were exposed to belimumab in all completed and ongoing studies.

Cumulative post-marketing exposure to belimumab is estimated to be 69,873 patient years] through 31 December 2017. This estimate reflects exposure to both the IV formulation (69,509 patient years) and the SC formulation (364 patient years).

The median (range) duration of exposure in study BEL114055 was 364 (28 to 374) days in the placebo group and 364 (81 to 377) days in the belimumab 10 mg/kg group. The duration of exposure in the pooled IV CRD adult studies was consistent with study BEL114055 (Table 19). The median duration of exposure was comparable between the placebo and belimumab groups in the pooled IV CRD adult studies and in study BEL114055.

Table 19. Study Agent Exposure through Week 52 (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Paediatric	
)uration of exposure (days)[a]	Placebo N=675	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
Mean (SD)	335.2 (97.13)	341.6 (94.51)	313.8 (106.66)	334.7 (78.95)
Median	369.0	371.0	364.0	364.0
Min, Max	28, 437	28, 450	(28, 374)	(81, 377)

a. For IV studies, duration was calculated as last infusion date - 1st infusion date + 28.
Only complete dates were used when calculating duration of exposure. First and last infusion dates were used, regardless of any missed doses.

Adverse events

An overall summary of the incidence of AEs reported during Part A (double-blind phase) of the study is provided in Table 20. The incidence of subjects experiencing at least 1 AE during Part A was 82.5% in the placebo group and 79.2% in the belimumab 10 mg/kg group. The incidence of subjects experiencing at least 1 SAE was 35.0% in the placebo group and 17.0% in the belimumab group.

Table 20. Adverse Event Summary (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

	Number (%) of Subjects				
	C1056/C1057/LBSL02 Pooled IV			BEL114055 IV Paediatric	
Subjects with at least one:	Placebo N=675	Belimumab 10 mg/kg N=674	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
AE	623 (92.3)	625 (92.7)	1354 (92.9)	33 (82.5)	42 (79.2)
Related AE	282 (41.8)	268 (39.8)	586 (40.2)	15 (37.5)	19 (35.8)
Serious AE	103 (15.3)	113 (16.8)	248 (17.0)	14 (35.0)	9 (17.0)
Severe[a] AE	99 (14.7)	96 (14.2)	220 (15.1)	12 (30.0)	6 (11.3)
Serious and/or severe[a] AE	138 (20.4)	147 (21.8)	328 (22.5)	17 (42.5)	10 (18.9)
resulting in study agent discontinuation	48 (7.1)	42 (6.2)	88 (6.0)	5 (12.5)	3 (5.7)
Death	3 (0.4)	6 (0.9)	11 (0.8)	1 (2.5)	0

Note: Only treatment-emergent AEs are summarized. MedDRA version 17.1 (Pooled IV CRD Adult Studies); MedDRA version 20.1 (study BEL114055).

a. Severe or life threatening for the IV CRD adult studies only.

The most frequent (>5% in any treatment group) AEs during Part A (double-blind phase) of study BEL114055 are shown by preferred term in Table 21 along with the integrated data for the pooled IV CRD adult studies.

Table 21. Adverse Events Occurring in >5% of Subjects in Any Treatment Group by Preferred Term (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

Preferred Term[a]	Number (%) of Subjects				
	C1056/C1057/LBSL02 Pooled IV			BEL114055 IV Paediatric	
	Placebo N=675	Belimumab 10 mg/kg N=674	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
Any Event	623 (92.3)	625 (92.7)	1354 (92.9)	33 (82.5)	42 (79.2)
Headache	137 (20.3)	142 (21.1)	306 (21.0)	11 (27.5)	7 (13.2)
Nasopharyngitis	42 (6.2)	55 (8.2)	111 (7.6)	8 (20.0)	9 (17.0)
Upper respiratory tract infection	126 (18.7)	112 (16.6)	269 (18.4)	8 (20.0)	6 (11.3)
Diarrhoea	61 (9.0)	81 (12.0)	184 (12.6)	3 (7.5)	7 (13.2)
Chest pain	2 (0.3)	1 (0.1)	1 (<0.1)	4 (10.0)	4 (7.5)
Herpes zoster	20 (3.0)	17 (2.5)	39 (2.7)	3 (7.5)	5 (9.4)
Nausea	78 (11.6)	98 (14.5)	205 (14.1)	3 (7.5)	5 (9.4)
Arthralgia	109 (16.1)	107 (15.9)	238 (16.3)	4 (10.0)	3 (5.7)
Epistaxis	14 (2.1)	14 (2.1)	28 (1.9)	3 (7.5)	4 (7.5)
Lupus nephritis	20 (3.0)	12 (1.8)	25 (1.7)	4 (10.0)	3 (5.7)
Abdominal pain	33 (4.9)	32 (4.7)	68 (4.7)	3 (7.5)	3 (5.7)
Cough	49 (7.3)	50 (7.4)	110 (7.5)	3 (7.5)	3 (5.7)
Gastroenteritis	31 (4.6)	25 (3.7)	63 (4.3)	3 (7.5)	3 (5.7)
Pharyngitis	20 (3.0)	31 (4.6)	63 (4.3)	3 (7.5)	3 (5.7)
Vomiting	44 (6.5)	46 (6.8)	109 (7.5)	4 (10.0)	2 (3.8)
Back pain	59 (8.7)	56 (8.3)	130 (8.9)	3 (7.5)	2 (3.8)
Leukopenia	15 (2.2)	25 (3.7)	49 (3.4)	3 (7.5)	2 (3.8)
Oropharyngeal pain	12 (1.8)	11 (1.6)	35 (2.4)	2 (5.0)	3 (5.7)
Pyrexia	50 (7.4)	63 (9.3)	129 (8.8)	3 (7.5)	2 (3.8)
Rash	34 (5.0)	36 (5.3)	99 (6.8)	1 (2.5)	4 (7.5)
Urinary tract infection	76 (11.3)	82 (12.2)	191 (13.1)	4 (10.0)	1 (1.9)
Dyspepsia	26 (3.9)	23 (3.4)	50 (3.4)	3 (7.5)	1 (1.9)

Neutropenia	8 (1.2)	16 (2.4)	30 (2.1)	1 (2.5)	3 (5.7)
Pain in extremity	27 (4.0)	40 (5.9)	87 (6.0)	2 (5.0)	2 (3.8)
Transaminases increased	2 (0.3)	1 (0.1)	4 (0.3)	1 (2.5)	3 (5.7)
Anaemia	31 (4.6)	30 (4.5)	63 (4.3)	3 (7.5)	0
Bronchitis	28 (4.1)	59 (8.8)	110 (7.5)	2 (5.0)	1 (1.9)
Fatigue	69 (10.2)	64 (9.5)	165 (11.3)	2 (5.0)	1 (1.9)
Influenza	42 (6.2)	46 (6.8)	101 (6.9)	3 (7.5)	0
Insomnia	34 (5.0)	44 (6.5)	83 (5.7)	3 (7.5)	0
Myalgia	47 (7.0)	44 (6.5)	98 (6.7)	1 (2.5)	2 (3.8)
Suicidal ideation	0	0	1 (<1)	3 (7.5)	0
Dizziness	42 (6.2)	35 (5.2)	84 (5.8)	0	2 (3.8)
Hypertension	55 (8.1)	44 (6.5)	90 (6.2)	2 (5.0)	0
Oedema peripheral	36 (5.3)	43 (6.4)	97 (6.7)	1 (2.5)	1 (1.9)
Sinusitis	51 (7.6)	47 (7.0)	93 (6.4)	1 (2.5)	1 (1.9)
Mouth ulceration	35 (5.2)	36 (5.3)	71 (4.9)	1 (2.5)	0
Arthritis	40 (5.9)	39 (5.8)	95 (6.5)	0	1 (1.9)
Depression	25 (3.7)	35 (5.2)	86 (5.9)	0	0

Note: Subjects only counted once per preferred term. Only treatment-emergent AEs are summarized. MedDRA version 17.1 (Pooled IV CRD Adult Studies); MedDRA version 20.1 (study BEL114055)

a. AEs are presented in descending order from the MedDRA preferred term with the highest overall incidence in study BEL114055 first and then in descending order for the remaining AEs in the pooled IV CRD adult studies that were not reported in study BEL114055. If the overall incidences for any two or more AE preferred terms are equal, the events are presented in alphabetical order.

Adverse Events by System Organ Class

In study BEL114055, SOCs with >20% of all subjects experiencing an AE were infections and infestations (70.0% placebo, 56.6% belimumab), gastrointestinal disorders (40.0% placebo, 34.0% belimumab), musculoskeletal and connective tissue disorders (32.5% placebo, 20.8% belimumab), nervous system disorders (27.5% placebo, 22.6% belimumab), skin and subcutaneous tissue disorders (22.5% placebo, 18.9% belimumab), and general disorders and administration site conditions (22.5% placebo, 17.0% belimumab) (Table 22). The incidences of AEs in the belimumab 10 mg/kg group were similar to or lower than those in the placebo group for the majority of SOCs. The SOCs with a notable difference (≥10% difference) between treatment groups were infections and infestations (70.0% placebo, 56.6% belimumab) musculoskeletal and connective tissue disorders (32.5% placebo, 20.8% belimumab), renal and urinary disorders (17.5% placebo, 7.5% belimumab), and metabolism and nutrition disorders (10.0% placebo, 0 belimumab).

The MAH states that the incidence of AEs by SOC in study BEL114055 were consistent with the pooled IV CRD adult studies, both in the belimumab group (all doses) and belimumab 10 mg/kg group (Table 22).

Table 22. Adverse Events by System Organ Class (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

System Organ Class[a]	Number (%) of Subjects				
	C1056/C1057/LBSL02 Pooled IV			BEL114055 IV Paediatric	
	Placebo N=675	Belimumab 10 mg/kg N=674	Belimumab (All Doses) N=1458	Placebo N=40	Belimumab 10 mg/kg N=53
Any Event	623 (92.3)	625 (92.7)	1354 (92.9)	33 (82.5)	42 (79.2)
Infections and infestations	444 (65.8)	472 (70.0)	1035 (71.0)	28 (70.0)	30 (56.6)
Gastrointestinal disorders	260 (38.5)	283 (42.0)	597 (40.9)	16 (40.0)	18 (34.0)
Musculoskeletal and connective tissue disorders	305 (45.2)	291 (43.2)	638 (43.8)	13 (32.5)	11 (20.8)
Nervous system disorders	235 (34.8)	244 (36.2)	525 (36.0)	11 (27.5)	12 (22.6)
Skin and subcutaneous tissue disorders	233 (34.5)	230 (34.1)	543 (37.2)	9 (22.5)	10 (18.9)
General disorders and administration site conditions	196 (29.0)	201 (29.8)	446 (30.6)	9 (22.5)	9 (17.0)
Respiratory, thoracic and mediastinal disorders	176 (26.1)	155 (23.0)	366 (25.1)	8 (20.0)	10 (18.9)
Injury, poisoning and procedural complications	115 (17.0)	132 (19.6)	288 (19.8)	7 (17.5)	10 (18.9)
Blood and lymphatic system disorders	90 (13.3)	88 (13.1)	190 (13.0)	7 (17.5)	7 (13.2)
Investigations	101 (15.0)	95 (14.1)	227 (15.6)	6 (15.0)	7 (13.2)
Renal and urinary disorders	77 (11.4)	70 (10.4)	143 (9.8)	7 (17.5)	4 (7.5)
Psychiatric disorders	80 (11.9)	100 (14.8)	219 (15.0)	6 (15.0)	3 (5.7)
Eye disorders	52 (7.7)	69 (10.2)	148 (10.2)	2 (5.0)	5 (9.4)
Immune system disorders	21 (3.1)	18 (2.7)	52 (3.6)	2 (5.0)	4 (7.5)
Reproductive system and breast disorders	65 (9.6)	71 (10.5)	149 (10.2)	4 (10.0)	1 (1.9)
Metabolism and nutrition disorders	66 (9.8)	77 (11.4)	156 (10.7)	4 (10.0)	0
Cardiac disorders	44 (6.5)	54 (8.0)	110 (7.5)	0	2 (3.8)
Vascular disorders	102 (15.1)	96 (14.2)	211 (14.5)	2 (5.0)	0
Endocrine disorders	9 (1.3)	11 (1.6)	29 (2.0)	1 (2.5)	0
Hepatobiliary disorders	18 (2.7)	14 (2.1)	34 (2.3)	0	1 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (3.3)	19 (2.8)	42 (2.9)	0	1 (1.9)
Ear and labyrinth disorders	33 (4.9)	26 (3.9)	78 (5.3)	0	0
Surgical and medical procedures	13 (1.9)	15 (2.2)	33 (2.3)	0	0
Pregnancy, puerperium and perinatal conditions	4 (0.6)	5 (0.7)	8 (0.5)	0	0
Congenital, familial and genetic disorders	2 (0.3)	2 (0.3)	4 (0.3)	0	0
Social circumstances	0	0	2 (0.1)	0	0

Note: Subjects only counted once per SOC. Only treatment-emergent AEs are summarized. MedDRA version 17.1 (Pooled IV CRD Adult Studies); MedDRA version 20.1 (study BEL114055).

a. AEs are presented in descending order from the MedDRA SOC with the highest overall incidence in study BEL114055 first and then in descending order for the remaining AEs in the pooled IV CRD adult studies that were not reported in study BEL114055. If the overall incidence for any two or more AE SOCs are equal, the events are presented in alphabetical order.

Drug-related AEs

The overall incidence of AEs considered by the investigator to be at least possibly related to study agent in study BEL114055 was 37.5% for the placebo group and 35.8% for the belimumab 10 mg/kg group. In the pooled data for the IV CRD adult studies, a total of 41.8% of subjects in the placebo group and 40.2% of subjects in the belimumab group experienced at least 1 AE that was considered by the investigator to be at least possibly related to study agent. Overall, the incidences of study agent related AEs were lower in study BEL114055 than that observed in the pooled IV CRD adult studies. The SOC with the highest incidence of drug-related AEs overall was infections and infestations in study BEL114055 (22.5% placebo, 11.3% belimumab) and in the pooled IV CRD studies (21.2% placebo, 20.9% belimumab).

When considered by preferred term in study BEL114055, drug-related AEs that occurred in more than 1 subject in either treatment group were headache (7.5% placebo, 3.8% belimumab), herpes zoster (5.0% placebo, 3.8% belimumab), blood immunoglobulin G decreased (5.0% placebo, 1.9% belimumab), fatigue (5.0% placebo, 0 belimumab), impetigo (0 placebo, 3.8% belimumab), nausea (5.0% placebo, 0 belimumab), neutropenia (0 placebo, 3.8% belimumab), transaminases increased (0 placebo, 3.8% belimumab), and urinary tract infection (5.0% placebo, 0 belimumab). Incidences in the belimumab 10 mg/kg group were similar to or lower than those in the placebo group for the majority of drug-related AEs in study BEL114055. Drug-related AEs with incidences that were lower (more than 1 subject difference) in the placebo group compared with the belimumab group were impetigo (0 placebo, 3.8% belimumab), transaminases increased (0 placebo, 3.8% belimumab), and neutropenia (0 placebo, 3.8% belimumab). In general, no clinically meaningful differences were observed between treatment groups with regard to drug-related AEs.

The most frequent drug-related AEs by preferred term (reported in ≥3% of subjects in any treatment group) in the pooled IV CRD studies were headache (5.3% placebo, 4.6% belimumab), nausea (3.9% placebo, 4.4% belimumab), upper respiratory tract infection (4.3% placebo, 4.1% belimumab), and urinary tract infection (2.2% placebo, 3.6% belimumab).

Serious adverse event / deaths / other significant events

Serious adverse events

In study BEL114055, SAEs were reported during Part A (double-blind phase) in 14 (35.0%) subjects in the placebo group and 9 (17.0%) subjects in the belimumab 10 mg/kg group (Table 23). The SOC with the highest incidence of SAEs was infections and infestations (12.5% placebo, 7.5% belimumab). With the exception of the infections and infestations SOC, the incidence of SAEs by SOC was <10% in both treatment groups. The incidence of SAEs by SOC in the IV belimumab 10 mg/kg group in study BEL114055 was generally consistent with the IV CRD adult studies, both in the belimumab group (all doses) and belimumab 10 mg/kg group.

Table 23. Serious Adverse Events by System Organ Class (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

System Organ Class[a]	Number (%) of Subjects				
	C1056/C1057/LBSL02 Pooled IV			BEL114055 IV Paediatric	
	Placebo N=675	Belimumab 10 mg/kg N=674	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
Any Event	103 (15.3)	113 (16.8)	248 (17.0)	14 (35.0)	9 (17.0)
Infections and infestations Renal	35 (5.2)	34 (5.0)	83 (5.7)	5 (12.5)	4 (7.5)
and urinary disorders Nervous	10 (1.5)	14 (2.1)	23 (1.6)	3 (7.5)	2 (3.8)
system disorders Gastrointestinal	8 (1.2)	14 (2.1)	25 (1.7)	2 (5.0)	2 (3.8)
disorders Musculoskeletal and	14 (2.1)	9 (1.3)	23 (1.6)	2 (5.0)	1 (1.9)
connective tissue disorders	14 (2.1)	12 (1.8)	29 (2.0)	2 (5.0)	1 (1.9)
Psychiatric disorders	3 (0.4)	8 (1.2)	12 (0.8)	3 (7.5)	0
Eye disorders	0	1 (0.1)	3 (0.2)	2 (5.0)	0
eneral disorders and administration site conditions	11 (1.6)	12 (1.8)	20 (1.4)	2 (5.0)	0
kin and subcutaneous tissue disorders	6 (0.9)	5 (0.7)	10 (0.7)	0	2 (3.8)
ood and lymphatic system disorders	7 (1.0)	10 (1.5)	14 (1.0)	1 (2.5)	0
Cardiac disorders	12 (1.8)	9 (1.3)	17 (1.2)	0	1 (1.9)
Hepatobiliary disorders	6 (0.9)	5 (0.7)	14 (1.0)	0	1 (1.9)
ury, poisoning and procedural complications	8 (1.2)	11 (1.6)	21 (1.4)	1 (2.5)	0
etabolism and nutrition disorders	3 (0.4)	1 (0.1)	4 (0.3)	1 (2.5)	0
espiratory, thoracic and mediastinal disorders	11 (1.6)	8 (1.2)	14 (1.0)	1 (2.5)	0
Vascular disorders	7 (1.0)	11 (1.6)	19 (1.3)	0	0
eproductive system and breast disorders	5 (0.7)	7 (1.0)	10 (0.7)	0	0
egnancy, puerperium and perinatal conditions	1 (0.1)	5 (0.7)	7 (0.5)	0	0
eoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4)	1 (0.1)	5 (0.3)	0	0
Immune system disorders	1 (0.1)	2 (0.3)	4 (0.3)	0	0
Investigations	1 (0.1)	3 (0.4)	3 (0.2)	0	0
Endocrine disorders	0	1 (0.1)	3 (0.2)	0	0
Ear and labyrinth disorders	0	0	1 (<0.1)	0	0
Surgical and medical procedures	1 (0.1)	0	0	0	0

Severe adverse events

The incidence of severe AEs in study BEL114055 was higher in the placebo group (30.0%) compared with the belimumab 10 mg/kg group (11.3%) (Table 24). When considered by SOC, severe AEs that occurred in more than 1 subject in either treatment group were infections and infestations (5.0% placebo, 5.7% belimumab), blood and lymphatic system disorders (7.5% placebo, 0 belimumab), renal and urinary disorders (2.5% placebo, 3.8% belimumab), general disorders and administration site conditions (5.0% placebo, 0 belimumab), and nervous system disorders (5.0% placebo, 0 belimumab). When considered by preferred term, severe AEs that occurred in more than 1 subject in either treatment group in study BEL114055 were lupus nephritis (2.5% placebo, 3.8% belimumab), chest pain (5.0% placebo, 0 belimumab), and thrombocytopenia (5.0% placebo, 0 belimumab).

The incidence of severe AEs by SOC in study BEL114055 was consistent with the pooled IV CRD adult studies (Table 24). According to the MAH, no clinically meaningful differences in severe AEs were observed between the two treatment groups in study BEL114055 compared with the IV CRD adult studies (Table 25).

Table 24. Severe Adverse Events by System Organ Class (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

System Organ Class[a]	Number (%) of Subjects			
	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Paediatric	
	Placebo N=675	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
Any Event	99 (14.7)	220 (15.1)	12 (30.0)	6 (11.3)
Infections and infestations	21 (3.1)	47 (3.2)	2 (5.0)	3 (5.7)
Blood and lymphatic system disorders	12 (1.8)	22 (1.5)	3 (7.5)	0
Renal and urinary disorders	11 (1.6)	19 (1.3)	1 (2.5)	2 (3.8)
Gastrointestinal disorders	17 (2.5)	32 (2.2)	1 (2.5)	1 (1.9)
eneral disorders and administration site	14 (2.1) 17 (2.5)	16 (1.1) 29 (2.0)	2 (5.0) 1 (2.5)	0 1 (1.9)
conditions	13 (1.9)	37 (2.5)	2 (5.0)	0
Musculoskeletal and connective tissue disorders	0	4 (0.3)	1 (2.5)	0
Nervous system disorders	4 (0.6)	9 (0.6)	1 (2.5)	0
Eye disorders	2 (0.3)	8 (0.5)	1 (2.5)	0
Investigations	2 (0.3)	7 (0.5)	0	1 (1.9)
Psychiatric disorders	9 (1.3)	12 (0.8)	1 (2.5)	0
Reproductive system and breast disorders	8 (1.2)	22 (1.5)	0	0
Respiratory, thoracic and mediastinal disorders	6 (0.9)	15 (1.0)	0	0
Skin and subcutaneous tissue disorders	8 (1.2)	10 (0.7)	0	0
Vascular disorders	4 (0.6)	13 (0.9)	0	0
Cardiac disorders	3 (0.4)	9 (0.6)	0	0
Injury, poisoning and procedural complications	3 (0.4)	6 (0.4)	0	0
Metabolism and nutrition disorders Hepatobiliary	1 (0.1)	3 (0.2)	0	0
disorders	1 (0.1) 0	3 (0.2) 3 (0.2)	0 0	0 0
Immune system disorders	1 (0.1)	2 (0.1)	0	0
oplasms benign, malignant and unspecified	0	2 (0.1)	0	0
(incl cysts and polyps)	0	2 (0.1)	0	0
Endocrine disorders				
Pregnancy, puerperium and perinatal conditions				
Ear and labyrinth disorders				
Surgical and medical procedures				

Note: Subjects only counted once per SOC. Only treatment-emergent AEs are summarized. Severe or life threatening for the adult CRD studies only.
MedDRA version 17.1 (Pooled IV CRD Adult Studies); MedDRA version 20.1 (study BEL114055).

a. AEs are presented in descending order from the MedDRA SOC with the highest overall incidence in study BEL114055 first and then in descending order for the remaining AEs in the pooled IV CRD adult studies that were not reported in study BEL114055. If

the overall incidence for any two or more adverse event SOCs are equal, the events are presented in alphabetical order.

The CHMP noted that the number of subjects experiencing severe adverse events is small, and conclusions are thereby hard to draw from the table above. Also, the definition used for severe adverse events ("*causing inability to carry out usual activities*") is somewhat vague and limits the value of this analysis.

Table 25. Severe Adverse Events Occurring in ≥2 Subjects in either Treatment Group in Study BEL114055 by Preferred Term (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

Preferred Term	Number (%) of Subjects			
	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Paediatric	
	Placebo N=675	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
Any Event	99 (14.7)	220 (15.1)	12 (30.0)	6 (11.3)
Lupus nephritis	3 (0.4)	7 (0.5)	1 (2.5)	2 (3.8)
Chest pain	1 (0.1)	0	2 (5.0)	0
Thrombocytopenia	2 (0.3)	6 (0.4)	2 (5.0)	0

Note: Subjects only counted once per preferred term. Only treatment-emergent AEs are summarized. Severe or life threatening for the adult CRD studies only.

MedDRA version 17.1 (Pooled IV CRD Adult Studies); MedDRA version 20.1 (study BEL114055).

Table includes severe AEs reported in ≥2 subjects in either treatment group in study BEL114055 and corresponding data are included from the pooled IV CRD adult studies.

Deaths

In study BEL114055, there were no deaths in the belimumab 10 mg/kg group during Part A (double-blind phase) of the study. One (2.5%) subject in the placebo group had a fatal SAE (acute pancreatitis). One death occurred in a subject receiving belimumab 10 mg/kg during Part B (open-label continuation phase) in study BEL114055 as of the 24 January 2018 data cut-off date.

This 17-year-old subject experienced gastroenteritis and septic shock 1 year and 325 days after receiving the first dose belimumab 10 mg/kg and 45 days after receiving the last dose of belimumab 10 mg/kg during Part B (open-label continuation phase). The subject was hospitalized and treated with sodium bicarbonate, calcium gluconate (calcium gluconate 10%), dopamine, meropenem, dextrose and electrolyte solution, omeprazole, sodium bicarbonate, ceftriaxone, sodium chloride, and sodium bicarbonate. The subject died due to cardio-respiratory arrest 47 days after the last dose of belimumab 10 mg/kg. The investigator considered that there was a reasonable possibility that the gastroenteritis, septic shock, and cardio-respiratory arrest were related to study agent. Other possible causes of these events included azathioprine.

Other significant adverse events

In study BEL114055, the overall incidence of AEs leading to discontinuation of study agent during Part A (double-blind phase) was 12.5% in the placebo group and 5.7% in the belimumab 10 mg/kg group (Table 26).

Table 26. Adverse Events Resulting in Study Agent Discontinuation

Preferred Term	Number (%) of Subjects			
	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Pediatric	
	Placebo N=675	Belimumab (All Doses) N=1458	Placebo N=40	Belimumab 10 mg/kg N=53
Any Event	48 (7.1)	88 (6.0)	5 (12.5)	3 (5.7)
Lupus nephritis	8 (1.2)	10 (0.7)	2 (5.0)	1 (1.9)
Hepatitis A	0	0	1 (2.5)	0
Hypertransaminasaemia	0	0	0	1 (1.9)
Pancreatitis acute	0	0	1 (2.5)[a]	0
Post herpetic neuralgia	0	0	0	1 (1.9)
Renal vasculitis	0	0	1 (2.5)	0

Note: Subjects only counted once per preferred term. Only treatment-emergent AEs are summarized.
MedDRA version 17.1 (Pooled IV CRD Adult Studies); MedDRA version 20.1 (study BEL114055).
Table includes AEs resulting in study agent discontinuation in at least 1 subject in either treatment group in study BEL114055 and corresponding data are included from the pooled IV CRD adult studies.
a. Fatal SAE

The CHMP noted that hypertransaminasaemia and post herpetic neuralgia (as discussed above) led to discontinuation of belimumab.

Adverse events of special interest (AESI)

Malignant neoplasms:

No subjects in either treatment group had a malignant neoplasm AESI during Part A (double-blind phase) of the study.

Infections:

The overall incidence of all infections of special interest was 13.2% in the belimumab group compared with 7.5% in the placebo group (Table 27). The incidences of all serious infections identified by the infections of special interest CMQ (2.5% placebo, 1.9% belimumab) and all opportunistic infections per MAH adjudication (0 placebo, 1.9% belimumab) were low for both treatment groups. No subjects in the placebo group and 1 (1.9%) subject in the belimumab group had a non-serious, non-opportunistic active tuberculosis AESI. One (1.9%) subject in the belimumab group had a non-serious, non-opportunistic candida infection. No subjects in either treatment group had a sepsis AESI.

The incidence of all herpes zoster infections was 7.5% in the placebo group and 9.4% in the belimumab 10 mg/kg group (Table 27). The incidence of serious herpes zoster was low and similar between treatment groups (2.5% placebo, 1.9% belimumab). No subjects in either treatment group had a serious opportunistic herpes zoster infection per GSK adjudication. There was 1 case of non-serious, recurrent herpes zoster in the belimumab group reported as an opportunistic infection. No cases of disseminated herpes zoster were reported in either treatment group. No subjects in either treatment group had an infection AESI that led to discontinuation of study agent.

The overall incidence of all infections of special interest AESI and herpes zoster was higher in both the placebo and belimumab groups in study BEL114055 compared with the IV CRD adult studies. According to the MAH, there were no clinically meaningful differences in serious infections of special interest AESI in the belimumab 10 mg/kg group in study BEL114055 compared with the belimumab group in the IV CRD adult studies.

Table 27. Infection Adverse Events of Special Interest by Category (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

Adverse Events of Special Interest Category	Number (%) of Subjects				
	C1056/C1057/LBSL02 Pooled IV			BEL114055 IV Paediatric	
	lacebo N=675	Belimumab 10 mg/kg N=674	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
All infections of Special Interest[a]	37 (5.5)	32 (4.7)	76 (5.2)	3 (7.5)	7 (13.2)
Serious[b]	5 (0.7)	9 (1.3)	19 (1.3)	1 (2.5)	1 (1.9)
All Opportunistic Infections per GSK Adjudication[c]	8 (1.2)	9 (1.3)	15 (1.0)	0	1 (1.9)
Serious	0	4 (0.6)	6 (0.4)	0	0
Opportunistic Infections per GSK adjudication excluding Tuberculosis and Herpes Zoster[c]	2 (0.3)	2 (0.3)	4 (0.3)	0	0
Serious	0	2 (0.3)	2 (0.1)	0	0
e Tuberculosis[a] Serious	0	0	0	0	1 (1.9)
-Opportunistic Serious	0	0	0	0	0
ortunistic[c] Serious	0	0	0	0	1 (1.9)
	0	0	0	0	0
	0	0	0	0	0
	0	0	0	0	0
erpes Zoster[a,d] Serious	25 (3.7)	21 (3.1)	46 (3.2)	3 (7.5)	5 (9.4)
n-Opportunistic Serious	3 (0.4)	3 (0.4)	7 (0.5)	1 (2.5)	1 (1.9)
portunistic[c] Serious	19 (2.8)	15 (2.2)	36 (2.5)	3 (7.5)	5 (9.4)
Recurrent	3 (0.4)	1 (0.1)	3 (0.2)	1 (2.5)	1 (1.9)
Disseminated Serious	6 (0.9)	7 (1.0)	11 (0.8)	0	1 (1.9)
	0	2 (0.3)	4 (0.3)	0	0
	6 (0.9)	4 (0.6)	6 (0.4)	0	1 (1.9)
	0	3 (0.4)	5 (0.3)	0	0
	0	2 (0.3)	4 (0.3)	0	0
Sepsis[a]	3 (0.4)	6 (0.9)	12 (0.8)	0	0
Serious	1 (0.1)	6 (0.9)	12 (0.8)	0	0

Note: Subjects only counted once per category. Only treatment-emergent AEs are summarized.
MedDRA version 17.1 (Pooled IV CRD Adult Studies); MedDRA version 20.1 (study BEL114055).

a. Per Custom MedDRA query.
b. Serious as identified by the infections of special interest CMQ; does not necessarily correlate with SAEs in the infections and infestations SOC.
c. Per sponsor adjudication.

Not all Herpes Zoster will be recurrent or disseminated.

The CHMP noted that according to this definition, infections were more common in the belimumab group compared to placebo and far more common than compared to adults. Although the number of cases is small, it is noted that the frequency of infections seems to be higher in children than in adults.

Depression/suicide/self-injury:

The incidence of depression/suicide/self-injury AESI per CMQ was 10.0% in the placebo group compared with 1.9% in the belimumab 10 mg/kg group.

Laboratory findings

Haematology:

The number and percentage of subjects in the belimumab 10 mg/kg group with either a Grade 3 or Grade 4 post baseline value for each hematology parameter were lower than or similar to those in the placebo group (Table 28). No clinically meaningful differences were observed for Grade 3 or Grade 4 haematology parameters between the belimumab and placebo groups in study BEL114055 compared with the IV CRD adult studies. The overall percentages of subjects with at least a 2 grade worsening from baseline in the belimumab 10 mg/kg group were lower than or similar to those in the placebo group.

Table 28. Summary of Subjects with Worst Toxicity Grade of 3 or 4: Hematology (ITT population, Study BEL114055 and Pooled IV CRD Adult Studies)

Hematology Parameter Worst Toxicity Grade	Number (%) of Subjects			
	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Paediatric	
	Placebo N=675	Belimumab (All Doses) N=1458	Placebo N=40	Belimumab 10 mg/kg N=53
Hemoglobin, n	674	1448	39	53
Grade 3	30 (4.5)	30 (2.1)	2 (5.1)	0
Grade 4	2 (0.3)	3 (0.2)	0	0
Leukocytes, n	674	1448	39	53
Grade 3	20 (3.0)	47 (3.2)	3 (7.7)	0
Grade 4	0	1 (<0.1)	0	0
Neutrophils, Segmented, n	674	1448	39	53
Grade 3	25 (3.7)	64 (4.4)	2 (5.1)	2 (3.8)
Grade 4	7 (1.0)	11 (0.8)	1 (2.6)	0
Platelets, n	673	1447	39	53
Grade 3	5 (0.7)	10 (0.7)	1 (2.6)	0
Grade 4	4 (0.6)	5 (0.3)	2 (5.1)	0

Parameters that do not have a Grade 3 or 4 value are not shown.

Liver function:

Laboratory changes with regards to liver function are shown in **Table 29** and Table 30.

Table 29. Summary of Subjects with Worst Toxicity Grade of 3 or 4: Liver Function Test (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

Liver Function Test Worst Toxicity Grade	Number (%) of Subjects			
	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Paediatric	
	Placebo N=675	Belimumab (All Doses) N=1458	Placebo N=40	Belimumab 10 mg/kg N=53
Alanine Aminotransferase, n	674	1448	39	53
Grade 3	2 (0.3)	3 (0.2)	0	0
Grade 4	2 (0.3)	0	1 (2.6)	1 (1.9)
Alkaline Phosphatase, n	674	1448	39	53
Grade 3	0	1 (<0.1)	0	0
Grade 4	1 (0.1)	0	0	0

Aspartate Aminotransferase, n	674	1448	39	53
Grade 3	2 (0.3)	5 (0.3)	0	0
Grade 4	1 (0.1)	4 (0.3)	1 (2.6)	2 (3.8)
Bilirubin, n	674	1448	39	53
Grade 3	0	1 (<0.1)	1 (2.6)	0
Grade 4	1 (0.1)	0	0	0
Gamma Glutamyl Transferase, n	674	1448	39	53
Grade 3	14 (2.1)	33 (2.3)	0	0
Grade 4	10 (1.5)	10 (0.7)	1 (2.6)	1 (1.9)

Table 30. Summary of Subjects with Worsening of at least 2 Grades from Baseline: Liver Function Test (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

Liver Function Parameter	Number (%) of Subjects			
	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Paediatric	
	Placebo N=675	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
Alanine Aminotransferase, n	673	1447	39	53
Any ≥2 grade shift	17 (2.5)	21 (1.5)	2 (5.1)	4 (7.5)
Grade 0 to 2	13 (1.9)	18 (1.2)	1 (2.6)	3 (5.7)
Grade 0 to 3	2 (0.3)	3 (0.2)	0	0
Grade 0 to 4	2 (0.3)	0	1 (2.6)	1 (1.9)
Alkaline Phosphatase, n	673	1447	39	53
Any ≥2 grade shift	3 (0.4)	2 (0.1)	0	0
Grade 0 to 2	2 (0.3)	1 (<0.1)	0	0
Grade 0 to 3	0	1 (<0.1)	0	0
Grade 0 to 4	1 (0.1)	0	0	0
Aspartate Aminotransferase, n	673	1447	39	53
Any ≥2 grade shift	10 (1.5)	19 (1.3)	1 (2.6)	5 (9.4)
Grade 0 to 2	7 (1.0)	12 (0.8)	0	3 (5.7)
Grade 0 to 3	2 (0.3)	3 (0.2)	0	0
Grade 0 to 4	1 (0.1)	3 (0.2)	1 (2.6)	2 (3.8)
Grade 2 to 4	0	1 (<0.1)	0	0
Bilirubin, n	673	1447	39	53
Any ≥2 grade shift	5 (0.7)	6 (0.4)	1 (2.6)	0
Grade 0 to 2	4 (0.6)	5 (0.3)	0	0
Grade 0 to 3	0	1 (<0.1)	1 (2.6)	0
Grade 0 to 4	1 (0.1)	0	0	0
Gamma Glutamyl Transferase, n	674	1448	39	53
Any ≥2 grade shift	31 (4.6)	57 (3.9)	1 (2.6)	3 (5.7)
Grade 0 to 2	17 (2.5)	33 (2.3)	0	2 (3.8)
Grade 0 to 3	3 (0.4)	5 (0.3)	0	0
Grade 0 to 4	4 (0.6)	6 (0.4)	1 (2.6)	1 (1.9)
Grade 1 to 3	4 (0.6)	11 (0.8)	0	0
Grade 1 to 4	1 (0.1)	0	0	0
Grade 2 to 4	2 (0.3)	2 (0.1)	0	0

Electrolytes:

In study BEL114055, 1 (2.6%) subject in the placebo group and 1 (1.9%) subject in the belimumab 10 mg/kg group had a Grade 4 post baseline value for an electrolyte parameter (hyponatremia and hypernatremia, respectively) (Table 31 and Table 32). The MAH states stat no clinically meaningful differences were observed for Grade 3 or Grade 4 electrolyte parameters between the belimumab and placebo groups in study BEL114055 compared with the IV CRD adult studies.

Table 31. Summary of Subjects with Worst Toxicity Grade of 3 or 4: Electrolytes (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

Electrolytes Worst Toxicity Grade	Number (%) of Subjects			
	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Paediatric	
	Placebo N=675	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
Hyperkalemia, n	674	1448	39	53
Grade 3	2 (0.3)	2 (0.1)	0	0
Grade 4	3 (0.4)	2 (0.1)	0	0
Hypernatremia, n	674	1448	39	53
Grade 3	1 (0.1)	1 (<0.1)	0	0
Grade 4	0	0	0	1 (1.9)
Hypocalcemia, n	562	1113	39	53
Grade 3	0	2 (0.2)	0	0
Hyponatremia, n	674	1448	39	53
Grade 3	0	1 (<0.1)	0	0
Grade 4	0	1 (<0.1)	1 (2.6)	0
Magnesium, n	674	1448	39	53
Grade 3	1 (0.1)	0	0	0
Phosphate, n	674	1448	39	53
Grade 3	5 (0.7)	16 (1.1)	0	0

Parameters that do not have a Grade 3 or 4 value are not shown.

Table 32. Summary of Subjects with Worsening of at least 2 Grades from Baseline: Electrolytes (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

Electrolytes	Number (%) of Subjects			
	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Paediatric	
	Placebo N=675	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
Hypercalcemia, n	562	1113	39	53
Any ≥2 grade shift	0	0	0	0
Hyperkalemia, n	673	1447	39	53
Any ≥2 grade shift	5 (0.7)	7 (0.5)	0	0
Grade 0 to 2	0	3 (0.2)	0	0
Grade 0 to 3	2 (0.3)	1 (<0.1)	0	0
Grade 0 to 4	3 (0.4)	2 (0.1)	0	0
Grade 1 to 3	0	1 (<0.1)	0	0
Hypernatremia, n	673	1447	39	53
Any ≥2 grade shift	2 (0.3)	10 (0.7)	0	3 (5.7)
Grade 0 to 2	1 (0.1)	9 (0.6)	0	2 (3.8)
Grade 0 to 3	1 (0.1)	1 (<0.1)	0	0
Grade 0 to 4	0	0	0	1 (1.9)
Hypocalcemia, n	562	1113	39	53
Any ≥2 grade shift	3 (0.5)	4 (0.4)	0	2 (3.8)
Grade 0 to 2	3 (0.5)	2 (0.2)	0	2 (3.8)
Grade 0 to 3	0	2 (0.2)	0	0
Hypokalemia, n	673	1447	39	53
Any ≥2 grade shift	5 (0.7)	13 (0.9)	0	1 (1.9)
Grade 0 to 2	5 (0.7)	13 (0.9)	0	1 (1.9)
Hyponatremia, n	673	1447	39	53
Any ≥2 grade shift	0	6 (0.4)	1 (2.6)	0
Grade 0 to 2	0	4 (0.3)	0	0
Grade 0 to 3	0	1 (<0.1)	0	0
Grade 0 to 4	0	1 (<0.1)	1 (2.6)	0
Magnesium, n	673	1447	39	53
Any ≥2 grade shift	2 (0.3)	8 (0.6)	0	0
Grade 0 to 2	2 (0.3)	8 (0.6)	0	0
Phosphate, n	673	1447	39	53
Any ≥2 grade shift	28 (4.2)	63 (4.4)	0	0
Grade 0 to 2	23 (3.4)	51 (3.5)	0	0
Grade 0 to 3	3 (0.4)	8 (0.6)	0	0
Grade 1 to 3	2 (0.3)	4 (0.3)	0	0

Urinalysis

For urinalysis parameters, the incidences of subjects in the belimumab 10 mg/kg group with a worsening of at least 2 grades from baseline were lower than or similar to that in the placebo group.

Immunoglobulins

Reduction of immunoglobulins (IgG, IgA, and IgM) is an expected pharmacologic effect of belimumab and was observed in the belimumab 10 mg/kg group compared with the placebo group in study BEL114055. This same pattern was seen in the pooled IV belimumab adult CRD studies between the IV belimumab and placebo groups (Table 33).

Table 33. Summary of Subjects with Worst Toxicity Grade of 3 or 4 or Worsening of at least 2 Grades from Baseline: Immunoglobulins (ITT Population, Study BEL114055 and Pooled IV CRD Adult Studies)

Immunoglobulin G	Number (%) of Subjects			
	C1056/C1057/LBSL02 Pooled IV		BEL114055 IV Paediatric	
	Placebo N=675	Belimumab (All Doses) N=1458	lacebo N=40	Belimumab 10 mg/kg N=53
Worst Toxicity Grade, n	664	1436	39	53
Grade 3	1 (0.2)	8 (0.6)	1 (2.6)	1 (1.9)
Grade 4	0	0	0	0
Worsening of at least 2 Grades from Baseline, n	664	1435	39	53
Any ≥2 grade shift	5 (0.8)	15 (1.0)	1 (2.6)	1 (1.9)
Grade 0 to 2	4 (0.6)	14 (1.0)	0	1 (1.9)
Grade 0 to 3	1 (0.2)	1 (<0.1)	0	0
Grade 1 to 3	0	0	1 (2.6)	0

The CHMP noted that no important differences are seen with regards to immunoglobulin levels.

Immunogenicity

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) of study BEL114055.

Safety in special populations

Adverse Events by Baseline Age and Cohort 3

An overall summary of the incidence of AEs by baseline age (5-11 years [Cohort 2] and 12-17 years [Cohorts 1 + 3]) and Cohort 3 alone reported during Part A (double-blind phase) of the study is provided in Table 34.

Table 34. Adverse Event Summary by Baseline Age Group and Cohort (ITT Population, Study BEL114055)

Subjects with at least one:	**Number (%) of Subjects**			
	BEL114055 IV Pediatric			
	Age Group: 5-11 years (Cohort 2)		**Age Group: 12-17 years (Cohort 1 and 3)**	
	Placebo **N=3**	Belimumab **10 mg/kg N=10**	Placebo **N=37**	Belimumab **10 mg/kg N=43**
At least 1 AE	3 (100.0)	10 (100.0)	30 (81.1)	32 (74.4)
At least 1 related AE	1 (33.3)	3 (30.0)	14 (37.8)	16 (37.2)
At least 1 serious AE	2 (66.7)	1 (10.0)	12 (32.4)	8 (18.6)
At least 1 severe AE	1 (33.3)	0	11 (29.7)	6 (14.0)
At least 1 serious and/or severe AE	2 (66.7)	1 (10.0)	15 (40.5)	9 (20.9)
At least 1 AE resulting in study agent discontinuation	1 (33.3)	0	4 (10.8)	3 (7.0)
Deaths	0	0	1 (2.7)	0

The CHMP noted that no important differences were seen for adverse events between the different age groups. The proportion of subjects with at least 1 AE was higher in the lower age group, but there was no difference when compared to placebo.

Safety related to drug-drug interactions and other interactions

Belimumab as a monoclonal antibody is not metabolized by the cytochrome P450 system. Thus, the types of drug interactions that occur between 1 or more drugs that compete for metabolism by this family of enzymes are not expected with belimumab. The population PK analysis including study BEL114055 evaluated impact of SLE standard of care concomitant medications. According to the MAH, no significant effects of concomitant medications were identified.

Post marketing experience

The cumulative post- marketing exposure to belimumab is estimated to be 69,873 patient years based on data from IQVIA [previously known as Intercontinental Medical Statistics (IMS) Health] through 31 December 2017. This estimate reflects exposure to both the IV formulation (69,509 patient years) and the SC formulation (364 patient years).

Routine pharmacovigilance is ongoing for belimumab for adult use. In addition, the RMP version 35 specifies risk minimization measures including ongoing surveillance of important identified and potential risks. Identified risks are hypersensitivity and infusion or injection-related systemic reactions and infections.

Potential risks are progressive multifocal leukoencephalopathy (PML), malignancies, immunogenicity, effects on immunizations, including interactions with live vaccines, and psychiatric events including depression and suicidality.

Areas requiring confirmation or further investigation are also noted in the effective EU RMP including pregnancy outcomes, the use of belimumab in elderly and paediatric patients, long-term data on B cell levels, SLE patient with severe active lupus nephritis or severe active central nervous system (CNS) lupus, and effect of stopping treatment/treatment holidays) and the risk of rebound phenomenon. Study BEL114055 addressed the further investigation in Paediatric patients.

Two belimumab registries are ongoing. HGS1006-C1124 (BEL116543/ SABLE) is a 5-year prospective observational registry to assess adverse events of interest and effectiveness in adults with active, autoantibody-positive SLE treated with or without BENLYSTA (belimumab). The BENLYSTA Pregnancy Registry is a prospective cohort study. The primary objective of this registry is to evaluate pregnancy and infant outcomes following BENLYSTA exposure and health status of live born infants at 1 year.

A cumulative and periodic report of post-marketing surveillance is submitted as scheduled in the belimumab Periodic Benefit-Risk Evaluation Report dated 03 May 2018.

At the time of submission of the variation, belimumab was not approved for paediatric use in any country. From the launch of BENLYSTA to 08 March 2018, the MAH has received 22 paediatric reports (4 post-marketing and 18 spontaneous) containing 56 AEs. Of the 22 reports, 18 were medically confirmed. The 22 paediatric reports were received from 10 countries (8 US, 11 EU, and 3 from other regions [1 from Norway and 2 from Brazil]). Post-marketing exposure for patients ages 0 to 17 is not available. Adverse events summarized by MedDRA SOCs in decreasing order of incidence were general disorders and administration site conditions (11 AEs), injury, poisoning and procedural complications (10 AEs, e.g., drug administered to patient of inappropriate age and off-label use), nervous system disorders (9 AEs), infections and infestations (7 AEs), musculoskeletal and connective tissue disorders(6 AEs), eye disorders (4 AEs), respiratory, thoracic and mediastinal disorders (2 AEs), and 1 AE in each of the blood and lymphatic system disorders, pregnancy, puerperium and perinatal conditions, psychiatric disorders, investigations, skin and subcutaneous tissue disorders, and surgical and medical procedures. None of the reported AEs were considered AEs of special interest and none had a fatal outcome. Of the 56 reported AEs, 12 were serious and 8 of the 12 SAEs were related to belimumab. Related SAEs were haemolysis,

coccidioidomycosis, pneumonia, SLE, arthritis, mental impairment, abortion spontaneous, and lupus pleurisy.

2.5.1. Discussion on clinical safety

The safety population in study BEL114055 includes 53 subjects exposed to belimumab. All randomised subjects received at least one dose of study drug and is identical to the ITT population. The proportion of subjects with AEs, serious AEs and severe AEs were lower in the belimumab groups compared to placebo.

The incidence of subjects experiencing at least 1 AE was 82.5% in the placebo group and 79.2% in the belimumab 10 mg/kg group. The incidence of subjects experiencing at least 1 SAE was 35.0% in the placebo group and 17.0% in the belimumab group.

AEs that occurred more commonly in the belimumab 10 mg/kg group and at an incidence at least 1% greater than that observed with placebo were diarrhea (7.5% placebo, 13.2% belimumab), herpes zoster (7.5% placebo, 9.4% belimumab), nausea (7.5% placebo, 9.4% belimumab), rash (2.5% placebo, 7.5% belimumab), neutropenia (2.5% placebo, 5.7% belimumab), and transaminases increased (2.5% placebo, 5.7% belimumab).

Among these AEs, the incidence of herpes zoster, neutropenia, and transaminases increased were higher in the belimumab group in study BEL114055 compared with the IV CRD adult studies. Leukopenia is included in the section 4.8 of the SmPC; however, herpes zoster and liver enzymes increase are not. One subject discontinued the study due to elevated liver enzymes. At the CHMP's request, the MAH has discussed these findings and, based on the data, the CHMP concluded that no SmPC updates were required.

Severe AEs within the SOCs injury, poisoning and procedural complications, eye disorders, immune system disorders, cardiac disorders, hepatobiliary disorders and neoplasms occurred more often in the belimumab group than in placebo. At the CHMP request the MAH presented those data, which included a case of pericarditis (considered a disease manifestation), a case of tachycardia (non-specific) and a case of papilloma (non-malignant). No safety signal emerged, and no SmPC changes were considered necessary by the CHMP.

Numerically more subjects in the belimumab group had a ≥2-grade shift in level of hypernatraemia and hypo-/hypercalcaemia. At the CHMP request, the MAH clarified that the derangement of the electrolytes were very mild and occurring on single occasions. Therefore the CHMP concluded that no SmPC updates were necessary.

The overall incidence of infections was 42/53 (79.2%) in the belimumab group and 33/40 (82.5%) in the placebo group. The overall incidence of all infections of special interest was 13.2% in the belimumab 10 mg/kg group compared with 7.5% in the placebo group. In the 5- to 11-year-old group, infections were reported in 8/10 patients receiving Benlysta and 3/3 patients receiving placebo, and serious infections were reported in 1/10 patients receiving Benlysta and 2/3 patients receiving placebo. In the 12- to 17-year-old group, infections were reported in 22/43 patients receiving Benlysta and 25/37 patients receiving placebo, and serious infections were reported in 3/43 patients receiving Benlysta and 3/37 patients receiving placebo. This information is included in section 4.8 of the SmPC.

In study BEL114055, there was one death in the placebo group (2.5%) during Part A (double-blind phase) of the study. The subject had a fatal SAE (acute pancreatitis). There was one death with belimumab in the open-label continuation phase (part B) of the study. This was a 17-year-old female who experienced gastroenteritis and septic shock 1 year and 325 days after receiving the first dose belimumab 10 mg/kg and 45 days after receiving the last dose of belimumab. Despite hospitalisation and treatment, the subject died due to cardio-respiratory arrest 47 days after the last dose of belimumab. The investigator

considered that there was a reasonable possibility that the gastroenteritis, septic shock, and cardio-respiratory arrest were related to study agent. Because of the mode of action for belimumab with an increased susceptibility for infections, there is reasonable causality with belimumab in this case.

Taking the mode of action of Benlysta into account, with suppression of B cells, the CHMP was concerned that treating children with Benlysta might lead to safety problems in a population who already have an increased susceptibility to infections. This concern was further supported by the fact that some children with SLE have complement defects and other deficiencies in the immune system leading to a furthermore increased risk for infections. In the observed data, there were no important differences in safety data between children aged 5-11 years and children aged 12 and above, however the data are limited in the 5-11 years group. At the CHMP request, the MAH committed to review the possibility to undertake a PASS within established registries, to further characterise the safety of Benlysta in children with SLE, with particular focus on infections. If such a study is considered feasible, then the PASS is to be included in the RMP as a category 3 commitment. The MAH has also committed to conduct targeted follow-up questionnaires on infections for paediatric patients 5 to 11 years of age. In addition, the MAH has strengthened the section 4.4 of the SmPC to indicate that the mechanism of action of belimumab could increase the risk for the development of infections in adults and children with lupus, including opportunistic infections, and that younger children may be at increased risk. The section 4.8 of the SmPC was also updated to mention that the safety data in children younger than 12 years of age (n=10) are limited and to include a specific paragraph on infections in the paediatric population.

Of note, the occurrence of fatal events and infections with belimimab is being reviewed as part of the ongoing PSUSA procedure (EMEA/H/C/PSUSA/00009075/201903) and will also be assessed with the submission of the data from the Annex II condition “The MAH shall provide the 1 year data report on a randomized, double-blind placebo-controlled large safety study, based on a protocol agreed with CHMP. The study will evaluate over a minimum of 1 year the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus. These adverse events of special interest include serious infections (including non serious and serious opportunistic infections and PML, malignancies (including non melanoma skin cancer), serious infusion and hypersensitivity reactions, and serious psychiatric events including mood disorders, anxiety and suicide” due in December 2019. The Committees will carefully review the data available and their potential implications on the paediatric population.

Considering the limited data on long-term safety (infections, other autoimmune diseases, immunogenicity and malignancies) in paediatric patients, this was included as missing information in the RMP and the MAH committed to the evaluation of safety (adverse of special interest, including infections, other autoimmune disease, immunogenicity, and malignancies) and efficacy data from paediatric studies.

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) of study BEL114055. The ADA incidence was low also in the adult Benlysta studies.

No important differences were seen with regards to immunoglobulin levels or adverse events between the different age groups. The proportion of subjects with at least 1 AE was higher in the lower age group, but there was no difference when compared to placebo.

The post-marketing experience of Benlysta in children is limited. There have been 22 reports regarding 56 AEs in paediatric patients. These include SLE-associated features strongly confounded by the disease itself. No new important safety signals were identified.

2.5.2. Conclusions on clinical safety

Overall, the safety profile observed in paediatric patients is largely similar to the safety profile observed in adults. A more favourable safety profile for Benlysta than for placebo was seen in the study in children, although these data are limited.

There are no important differences in the observed safety data between children aged 5-11 years and children aged 12 and above. However, the data are limited in the 5-11 years group. At the CHMP request, the MAH has strengthen the wording in the SmPC to indicate that the mechanism of action of belimumab could increase the risk for the development of infections in children with lupus, including opportunistic infections, and that younger children may be at increased risk.

Considering the risk of infections with Benlysta, the MAH committed at the CHMP request to review the possibility to undertake a PASS within established registries, to further characterise the safety of Benlysta in children with SLE, with particular focus on infections. If such a study is considered feasible, then the PASS is to be included in the RMP as a category 3 commitment. This commitment was considered adequate by the CHMP to monitor the safety in the paediatric population.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 35 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 35 with the following content:

Safety concerns

Table 35 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity and Infusion or injection related systemic reactions Infections Psychiatric events including depression and suicidality
Important potential risks	Progressive multifocal leukoencephalopathy Malignancies Immunogenicity Effects on Immunisations, including interactions with Live Vaccines
Missing information	Limited data in pregnant and lactating patients

	Limited data in elderly patients Limited data on long-term safety (infections, other autoimmune diseases, immunogenicity and malignancies) in paediatric patients Effect of long-term B cell reduction on safety Lack of data in SLE patients with severe active lupus nephritis or severe active CNS lupus Lack of data on effect of stopping treatment (treatment holidays) and on risk of rebound phenomenon

Pharmacovigilance plan

Table 36 On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Large Safety Study HGS1006-C1113 (BEL115467/BASE) Ongoing	The study will evaluate over a minimum of 1 year the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus. These adverse events of special interest include serious infections (including nonserious and serious opportunistic infections and PML, malignancies (including nonmelanoma skin cancer), serious infusion and hypersensitivity reactions, and serious psychiatric events including mood disorders, anxiety and	Events of special interest: mortality, selected psychiatric events/suicidality events, serious infusion and hypersensitivity reactions, serious /opportunistic infections, and malignancy.	One-year data report.	31Dec2019

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	suicide			
5-Year Safety Registry HGS1006-C1124 (BEL116543/SABLE) Ongoing	To provide a data report on a long-term controlled safety registry where all patients are followed for a minimum of 5 years, based on a protocol agreed with CHMP. The safety registry will evaluate the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus. These adverse events of special interest include serious infections (including opportunistic infections and PML), selected serious psychiatric events, and malignancies (including non-melanoma skin cancer).	Long-term safety	Final CSR	28Feb2026
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
None				
Category 3- Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Pregnancy Registry HGS1006-C1101 (BEL114256) Ongoing	Prospective cohort study. Primary objectives are to evaluate pregnancy and infant outcomes following Benlysta exposure and health status of live infants at 1 year	Safety in pregnancy	Interim report Final CSR	20Sep2019 30Apr2022
Lupus Nephritis Study HGS1006-C1121 (BEL114054) Ongoing	To evaluate the efficacy and safety of belimumab plus standard of care versus placebo in adult subjects with active lupus nephritis	Safety in subjects with lupus nephritis	Final CSR	July 2020
Elderly Subject Analyses BEL116559 Ongoing	Pooled analyses of elderly patients (aged ≥ 65 years) who participated in select belimumab clinical trials	Safety in elderly subjects	Report 1 Report 2 Report 3 Report 4 Report 5	Sep2013 Jul2016 Jul2017 Dec2019 Feb2026
Treatment Holiday Study BEL116027 Ongoing	To assess the effect of a 24-week withdrawal followed by a 28-week re-introduction of belimumab 10mg/kg plus standard of care on immunogenicity, markers of biological activity, efficacy, and safety in subjects with stable low SLE disease activity. In addition, this study will assess rebound phenomenon in subjects with any disease level of SLE who have permanently withdrawn from further belimumab	Assess the safety of discontinuation and re-introduction of belimumab	Final CSR	Sep2019

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	treatment.			
Large Safety Study HGS1006-C1113 (BEL115467/BASE) Ongoing	The study will evaluate over a minimum of 1 year the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus. These adverse events of special interest include serious infections (including nonserious and serious opportunistic infections and PML, malignancies (including nonmelanoma skin cancer), serious infusion and hypersensitivity reactions, and serious psychiatric events including mood disorders, anxiety and suicide	Events of special interest: mortality, selected psychiatric events/suicidality events, serious infusion and hypersensitivity reactions, serious /opportunistic infections, and malignancy	a) Interim report of 2000 subjects with one-year exposure b) Interim report of 2 years malignancy and mortality follow-up c) Interim report of 3 years malignancy and mortality follow-up d) Interim report of 4 years malignancy and mortality follow-up e) Final CSR 5 years malignancy and mortality follow-up	31Dec2016 31Dec2020 31Dec2021 31Dec2022 31Dec2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Pediatric Safety Study BEL114055/PLUTO-open label Ongoing	To evaluate the safety and tolerability, pharmacokinetics and efficacy of belimumab and the effects of belimumab on the quality of life in the pediatric SLE population.	Long-term safety, efficacy and tolerability in pediatric population, including careful monitoring of infections	Final End of Study CSR	31Dec2028
5-Year Safety Registry HGS1006-C1124 (BEL116543/SABLE) Ongoing	To provide a data report on a long-term controlled safety registry where all patients are followed for a minimum of 5 years, based on a protocol agreed with CHMP. The safety registry will evaluate the incidence of all-cause mortality and adverse events of special interest in patients with systemic lupus erythematosus. These adverse events of special interest include serious infections (including opportunistic infections and PML), selected serious psychiatric events, and malignancies (including non-melanoma skin cancer).	Long-term safety	Yearly Interim Reports	28Feb2014 through 28Feb2025
Ongoing	To review the possibility to undertake a PASS within established	Safety in pediatric patients	Feasibility assessment report	19 November 2019

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	registries, to further characterise the safety of Benlysta in children with SLE, with particular focus on infections. If such a study is considered feasible, then the PASS is to be included in the RMP as a category 3 commitment.			

Risk minimisation measures

Table 37 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Hypersensitivity or Injection related reactions	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.8 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Analysis of additional safety data that may arise from ongoing studies, including serious infusion and hypersensitivity reactions being a separate safety endpoint in the 1-year placebo-controlled safety study (BEL115467/BASE) Additional pharmacovigilance activities: None
Infections	Routine risk minimisation measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimisation	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire on infections for patients 5 to 11 years old. Analysis of additional safety data that may arise from ongoing studies, including serious infections and infections of special interest

	measures None	from ongoing open-label study BEL114055 in the pediatric population. Evaluation of data on serious infections including opportunistic infections, tuberculosis, and herpes zoster from 1-year placebo-controlled safety study (BEL115467/BASE) and long-term safety registry (BEL116543/SABLE) Additional pharmacovigilance activities: None
Psychiatric events including depression and suicidality	Routine risk minimization measures: SmPC Sections 4.4, 4.8 This is a prescription only medicine. Additional risk minimization measures: DHPC distribution in April 2019.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Analysis of additional safety data that may arise from ongoing studies Specific adverse reaction follow-up questionnaires for Depression and Suicidality: Belimumab and Possible Suicidal Behavior/Suicidal Ideation (Including Potential Self Harm such as Intentional Overdose) Additional pharmacovigilance activities: Prospective assessment of suicidality in randomised controlled trials (including the 1-year placebo-controlled safety study [BEL115467/BASE]
Important Potential Risks		
Progressive Multifocal Leukoencephalopathy	Routine risk minimization measures: The IV and SC SmPC Routine activity includes appropriate labelling. Section 4.4 Special warnings and precautions for use of the SmPCs contains the EMA SmPC text agreed: Progressive multifocal leukoencephalopathy (PML) has been reported with Benlysta treatment for SLE. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if	Rountine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Follow-up Questionnaire for PML Analysis of additional safety data that may arise from ongoing studies Evaluation of data on opportunistic infections, including PML, tuberculosis, and herpes zoster from 1-year placebo-controlled safety study (BEL115467/BASE) and long-term safety registry (BEL116543/SABLE) Additional pharmacovigilance activities: None

	such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded. This is a prescription only medicine. Additional risk minimization measures: None	
Malignancies	Routine risk minimization measure: SmPC Section 4.4 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Analysis of additional safety data that may arise from ongoing studies Evaluation of data on malignancies, including haematological malignancies and NMSC from 1-year placebo-controlled safety study (BEL115467/BASE) and long-term safety registry (BEL116543/SABLE) Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimization measures: SmPC Section 5.1 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation of safety data and monitoring of immunogenicity data from ongoing studies Additional pharmacovigilance activities: Analyze the occurrence of antibody formation to belimumab associated with safety findings in subjects receiving belimumab in a controlled setting
Effect on Immunisations	Routine risk minimization measures: SmPC Section 4.4 This is a prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation of safety data Additional pharmacovigilance activities: None

	Additional risk minimization measures: None	

Missing Information		
Limited data in pregnant and lactating patients	Routine risk minimization measures: SmPC Section 4.6, 5.3 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Analysis of additional safety data that may arise from ongoing studies Additional pharmacovigilance activities: Ongoing Benlysta Pregnancy Registry in selected countries where belimumab is marketed and the long-term safety registry (BEL116543/SABLE)
Limited data in elderly patients	Routine risk minimization measures: SmPC Section 4.2, 5.2 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Evaluation of safety and efficacy data from ongoing and future studies Additional pharmacovigilance activities: Analysis plan for BEL116559 has been agreed with EMA
Limited data on long-term safety in paediatric patients	Routine risk minimization measures: SmPC Section 4.2 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Additional pharmacovigilance activities: Evaluation of safety (adverse of special interest, including infections, other autoimmune disease, immunogenicity, and malignancies) and efficacy data from these studies including follow-up of enrolled subjects in BEL114055 until 10 years after their first belimumab dose SLE paediatric studies with EMA in IV and SC PIP

Effect of long-term B cell reduction on safety	Routine risk minimization measures: SmPC Section 4.4 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Lack of data in SLE patients with severe active lupus nephritis or severe active CNS lupus	Routine risk minimization measures: SmPC Section 4.4, 5.1 This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: Evaluation of safety data from an ongoing study in Lupus Nephritis (BEL114054)
Lack of data on effect of stopping treatment (treatment holidays) and on risk of rebound phenomenon	Routine risk minimization measures: This is a prescription only medicine. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: Evaluation of safety and efficacy data from an ongoing Treatment holiday/Rebound effect study (BEL116027)

2.7. Update of the Product information

Benlysta powder for concentrate for solution for infusion

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Section 6.6 of the SmPC was updated to include instructions on a reduced dilution volume for paediatric patients. A reciprocal statement has been added to the 'Information for healthcare professionals' at the end of the PL.

Benlysta solution for injection in pre-filled pen and pre-filled syringe, 200 mg

Sections 4.2, 4.4, 5.1, 5.2 and 6.4 of the SmPC to reflect the paediatric data available for the intravenous formulation.

The Annex IIIA and the Package Leaflet is updated accordingly.

Changes were also made to the PIs for both formulations to bring them in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP:

- Section 4.4 of the SmPC for both formulations was updated to include a statement on traceability in line with the Guideline on good pharmacovigilance practices (GVP) (EMA/168402/2014 Corr) P.II.B.1.1.4. RMP part V "Risk minimisation measures". A reciprocal statement has been added to section 2 of the PL.
- Among those changes, section 6.4 of the SmPC an Section 5 of the PL for Benlysta solution for injection in pre-filled pen and pre-filled syringe, 200 mg were updated to include in-use storage conditions proposed for alignment with the QRD template (which states that the in-use shelf life should be included in this section) and consistency with the approved 'Instructions for Use' (IFU) which already included the inuse storage conditions. The stability data to support the in-use storage conditions were submitted in modules 3.2.P.2.6 (section 4) and 3.2.P.8.1 (section 7) of the Benlysta subcutaneous line extension (EMEA/H/C/002015/X/0046/G).

2.7.1. User consultation

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

"Consultation with target patient groups" was conducted as part of the original Marketing Authorisation Application (MAA). The changes to the package leaflet are minimal and do not require further user consultation with target patient groups.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Benlysta (belimumab) is included in the additional monitoring list as a Post-authorisation safety study is on-going.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

SLE predominantly affects female patients between the ages of 15 and 40, and in approximately 10-20% of SLE patients, disease onset occurs prior to 20 years of age [Aggarwal, 2015; Kamphuis, 2010; Klein-Gitelman, 2002; Malattia, 2013]. Regardless of age of onset or time of diagnosis, SLE patients share many immunogenetic and serologic similarities [Aggarwal, 2015; Barron, 1993; Livingston, 2012; Mina, 2013]. It has been reported that there are some differences in clinical features in childhood-onset SLE [Aggarwal, 2015; Brunner 2008; Costallat, 1994; Mina, 2013; Tucker, 1995].

Prepubertal onset of SLE is uncommon, and more often associated to rare monogenic variants, for example mutations in the complement system. Paediatric SLE patients tend to have more active disease

both at the time of diagnosis and over time [Kamphuis, 2010; Livingston, 2012; Mina, 2013]. In a study by Brunner et al, the mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score in Paediatric SLE patients at diagnosis was 1.7 times the score in adult SLE patients (16.8 vs. 9.3, respectively) [Brunner, 2008]. SLE in children can be associated with more rapid accrual of damage and may have a higher degree of morbidity compared with SLE in adult populations [Brunner, 2008; Kamphuis, 2010; Levy, 2012; Malattia, 2013; Tucker, 2008]. In a global study by the PRINTO, damage was present in 58.2% of the patients who had disease duration more than 5 years [Gutiérrez-Suárez, 2006]. The range of organ involvements in Paediatric SLE is generally similar to adult SLE with some manifestations more prevalent in children, such as renal lupus, malar rash, seizures, oral ulcers, hemolytic anemia, and thrombocytopenia [Aggarwal, 2015; Barron, 1993; Brunner, 2008; Fonseca, 2018; Mina, 2013; Webb, 2011]. Glomerulonephritis and neurologic involvement represent significant disease burden in SLE and occurred at higher frequency in Paediatric SLE [Amaral, 2014; Ambrose, 2016; Barron, 1993; Fish, 1977; Fonseca, 2018; King, 1977; Tarr, 2015; Tucker, 2008]. Growth failure and delayed puberty are complications of SLE specific to children that may have a serious psychological impact. The frequency of both events increased significantly with the increase in disease duration [Gutiérrez-Suárez, 2006].

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

SLE incidence and prevalence increase with age during childhood, and diagnosis is uncommon in children aged ≤9 years [Hiraki, 2012; Lim, 2009; Nightingale, 2007; Somers, 2007]. In a US study of claims data, the incidence of SLE was 0.13, 1.92 and 6.40 per 100,000 per year in children aged 3 to <6, 9 to <12 and 15 to <18 years of age [Hiraki, 2012]. In a population based study in the United Kingdom, 0 and 1 incident case were identified in children aged <10, and 10-19 respectively [Hopkinson, 1993]. A limitation of these estimates is that they are based on small sample sizes and are therefore subject to some uncertainty.

3.1.2. Available therapies and unmet medical need

Currently no treatments are approved for SLE in Paediatrics. The clinical evidence of effective treatment of childhood rheumatic diseases including SLE is generally based on anecdotal reports [Lehman, 1997]. Similar to adult-onset disease, Paediatric SLE is a chronic disease for which there is no cure. All patients require life-long treatment with a variety of medications for disease control. Generally, children are treated with the same agents which have been used in the adult population such as corticosteroids, anti-malarial agents, non-steroidal anti-inflammatory drugs (NSAIDs), cytotoxic agents, and immunosuppressive/immunomodulatory agents [Brocard, 2005; Chatham, 2001; Houssiau, 2004; Midgley, 2014; Petri, 2001; Reveille, 2001; Ruiz-Irastorza, 2001; Wallace, 2002].

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

3.1.3. Main clinical studies

The belimumab clinical development program that led to the IV BENLYSTA marketing approval only included patients aged 18 years or older.

The IV belimumab Paediatric study agreed in the PIP, BEL114055, consists of three phases as summarized in the table below. The study enrolled 93 subjects randomised to treatment with belimumab or placebo. Eligible subjects for the study was 5 to 17 years of age and had clinically active SLE disease, defined as a SELENA SLEDAI disease activity score of ≥6 at screening. Subjects had to have 4 or more of the 11 American College of Rheumatology (ACR) criteria for the classification of SLE either at screening or in the past. Subjects also had to have positive test result for anti-nuclear antibody (ANA) titer ≥1:80 and/or anti-dsDNA ≥30 IU/mL serum antibody.

Key exclusion criteria included active central nervous system (CNS) lupus or severe renal deficiency.

Belimumab concentrations were collected in 53 Paediatric SLE subjects (study BEL114055, part A) and analysed with a population PK analysis. PK samples were measured on the day of dosing (Days 0, 14, 28, 56, 168, and 364) and a minimum of 6 samples per individual were collected. The belimumab 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 Paediatric population. Structural model parameters and covariate effects were estimated using Paediatric data only.

The primary efficacy endpoint was SRI4 response at week 52. SRI4 is defined as: ≥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 at the time of assessment (i.e., at Week 52). The study was only powered for descriptive efficacy.

A brief description of the study is shown in Table 38.

Table 38. IV Belimumab Paediatric Study: BEL114055

Phase of study	Description/Status	Treatment Details (Test Products); Dosage Regimen; Duration of Therapy
Part A	Double-blind phase: concluded; 93 subjects: 13, 5-11 years old 80, 12-17 years old	Belimumab 10 mg/kg or Placebo; IV infusion; Day 0, 14, 28 then every 4 weeks; 52 weeks + background standard of care therapy
Part B	Long-term open-label continuation phase: ongoing	Belimumab 10 mg/kg; IV infusion; Monthly + background standard of care therapy
Part C	Long-term safety follow-up: ongoing	Standard of care therapy

3.2. Favourable effects

The belimumab population PK model for the Paediatric population described the data reasonably well and was similar to the population PK model described for the adult SLE population. The steady-state exposure

parameters Cmax, Cmin, Cavg, and AUC were similar between the age and weight groups with a trend towards slightly higher exposure in the older compared to the younger age group. Exposure parameters for both Paediatric age groups and the overall Paediatric population were consistent with the adult exposure parameters with largely overlapping confidence intervals. Geometric mean Cmax,ss=305/317/311 [µg/mL] and AUC=2569/3126/2811 [day µg/mL] in 5-11 years old, 12-17 years old, and adults, respectively. The proposed dosing regimen of 10 mg/kg to all SLE patients was endorsed by the CHMP.

The primary clinical efficacy endpoint, SRI4 response at week 52, was achieved by 28/53 subjects in the belimumab group (52.8%) and 17/40 subjects (43.6%) in the placebo group. The difference was not statistically significant, but numerically the response rate was similar to the response rate in the phase 3 studies in adults (43.2% in belimumab vs 33.8% in placebo in C1056 and and 57.6% in belimumab vs 43.6% in placebo in C1057). Also for SRI6, the response rate was numerically higher in the belimumab group vs placebo, although the differences were smaller than compared to the phase 3 trials in adults. The proportion of subjects with PRINTO/ACR response was higher in the belimumab group compared to placebo, regardless if 50% or 30% improvement was used in the definition.

Among other secondary endpoints, the percent change in parentGA from baseline was numerically higher in the belimumab group.

3.3. Uncertainties and limitations about favourable effects

SLE in children is very rare, and an adequately powered study to address these safety concerns is not considered feasible.

SLE with pre-pubertal onset is uncommon and more often associated to rare monogenic variants which sometimes lead to severe forms of the disease and an increased susceptibility to infections. In study BEL114055, only 13 subjects were aged 5-11 years out of which 10 were treated with Benlysta. Although data are limited, there were no important differences in the clinical study in disease characteristics between children and adults, nor between children aged 5-11 and older children aged ≥12 years. Whilst the data is sparse the CHMP acknowledges the high unmet medical need and that the efficacy response in the 10 patients aged 5-11 treated with belimumab numerically similar to the older age group of 12-18, supporting extrapolation of efficacy.

The SRI response rate in the subpopulation of subjects with high disease activity defined as low complement C3/C4 levels or high anti-ds-DNA levels (target population according to current indication) was numerically lower for belimumab (8/22 subjects, 36.4%) than for placebo (6/16 subjects, 37.5%). However, the CHMP was of the opinion that the small study size does not allow any conclusions to be drawn from the subgroup analyses. Indeed, the study was not powered for any formal comparisons between randomised treatments.

There was no steroid-sparing effect found for belimumab.

3.4. Unfavourable effects

The incidence of subjects experiencing at least 1 AE was 82.5% in the placebo group and 79.2% in the belimumab 10 mg/kg group. The incidence of subjects experiencing at least 1 SAE was 35.0% in the placebo group and 17.0% in the belimumab group.

The incidence of severe AEs in study BEL114055 was higher in the placebo group (30.0%) compared with the belimumab 10 mg/kg group (11.3%). Severe AEs that occurred in more than 1 subject in either treatment group were infections and infestations (5.0% placebo, 5.7% belimumab), blood and lymphatic system disorders (7.5% placebo, 0 belimumab), renal and urinary disorders (2.5% placebo, 3.8%

belimumab), general disorders and administration site conditions (5.0% placebo, 0 belimumab), and nervous system disorders (5.0% placebo, 0 belimumab).

In study BEL114055, there was one death in the placebo group (2.5%) during Part A (double-blind phase) of the study. The subject had a fatal SAE (acute pancreatitis). There was one death with belimumab in the open-label continuation phase (part B) of the study.

The overall incidence of infections was 42/53 (79.2%) in the belimumab group and 33/40 (82.5%) in the placebo group. The overall incidence of all infections of special interest was 13.2% in the belimumab 10 mg/kg group compared with 7.5% in the placebo group. At the CHMP request, the MAH has strengthened the section 4.4 of the SmPC to indicate that the mechanism of action of belimumab could increase the risk for the development of infections in adults and children with lupus, including opportunistic infections, and that younger children may be at increased risk.

Overall, the safety profile observed in paediatric patients is largely similar to the safety profile observed in adults.

3.5. Uncertainties and limitations about unfavourable effects

Taking the mode of action of Benlysta into account, with suppression of B cells, the CHMP was concerned that treating children with Benlysta might lead to safety problems in a population who already have an increased susceptibility to infections. This concern was further supported by the fact that some children with SLE have complement defects and other deficiencies in the immune system leading to a furthermore increased risk for infections. In the observed data, there were no important differences in safety data between children aged 5-11 years and children aged 12 and above, however the data are limited in the 5-11 years group. At the CHMP request, the MAH committed to review the possibility to undertake a PASS within established registries, to further characterise the safety of Benlysta in children with SLE, with particular focus on infections. If such a study is considered feasible, then the PASS is to be included in the RMP as a category 3 commitment. The MAH has also committed to conduct targeted follow-up questionnaires on infections for paediatric patients 5 to 11 years of age. In addition, the MAH has strengthened the section 4.4 of the SmPC to indicate that the mechanism of action of belimumab could increase the risk for the development of infections in adults and children with lupus, including opportunistic infections, and that younger children may be at increased risk. The section 4.8 of the SmPC was also updated to mention that the safety data in children younger than 12 years of age (n=10) are limited and to include a specific paragraph on infections in the paediatric population. Those measures were considered adequate by the CHMP in view of the extension of indication in the paediatric population.

3.6. Effects Table

Table 39. Favourable Effects for Benlysta in paediatric SLE:

Effect	Short description	Unit	Age 5-11 Years	Age 12-17 Years	Adults	Uncertainties / Strength of evidence	References
Favourable Effects							
Cmax,ss (µg/mL)	Maximum steady-state concentration	Geometric mean (95% CI)	305 (267-350)	317 (288-350)	311 (306-316)	Model predicted	Table 4
Cmin,ss (µg/mL)	Minimum steady-state concentration	Geometric mean (95% CI)	42 (30-60)	52 (43-63)	46 (44-48)	Model predicted	Table 4
AUC,ss (day·µg/mL)	Steady-state daily exposure	Geometric mean (95% CI)	2569 (1992-3314)	3126 (2765-3533)	2811 (2734-2890)	Model predicted	Table 4

Table 40. Unfavourable Effects for Benlysta in paediatric SLE:

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Adverse events	Total AEs	N (%)	42/53 (79.2%)	33/40 (82.5%)	Small study size	Table 22
Severe AEs	Total sAES	N (%)	6/53 (11.3%)	12/40 (30.0%)	Small study size	Table 22
Infections	All infections	N (%)	30/53 (56.6%)	28/40 (70.0%)	Small study size	Table 22
Serious infections	Serious infections	N (%)	4/53 (7.5%)	5/40 (12.5%)	Small study size	Table 23
Infections of special interest	AESI	N (%)	7/53 (13.2%)	3/40 (7.5%)	Small study size	Table 27
Herpes zoster		N (%)	5/53 (9.4%)	3/40 (7.5%)	Small study size	Table 27
Transaminases increased		N (%)	3/53 (5.7%)	1/40 (2.5%)	Small study size	Table 21

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In this application, the MAH seeks approval for treatment of paediatric patients with SLE aged 5-17 years. The basis for the application is a phase 2 study, agreed in the PIP at the approval of Benlysta. The study was not powered for formal comparisons between Benlysta and placebo, and the efficacy and safety needs to be extrapolated to children using PK data and a numerical comparison of the clinical results between the paediatric and adult studies.

An adequate population PK analysis of the Paediatric study show that the PK properties of belimumab in the Paediatric population are similar to those in the adult population. Model predicted belimumab plasma exposure display similar levels between the adult and Paediatric populations across all body weights. The proposed dosing regimen of 10 mg/kg to all SLE patients was endorsed by the CHMP.

The most important favourable clinical effect is the SRI response rate, which was numerically in favour of Benlysta. In the proposed target population of children with high disease activity defined as low complement and/or anti-ds-DNA antibodies, Benlysta was numerically inferior to placebo. However, the CHMP was of the opinion that the small study size does not allow any conclusions to be drawn from the subgroup analyses. Indeed, the study was not powered for any formal comparisons between randomised treatments.

The benefit of treatment with Benlysta in children from study BEL114055 could be considered as modest as for the adult population.

At the approval of Benlysta it was concluded that the effect of belimumab was shown in a population with mainly mucocutaneous and musculoskeletal involvement. The rather modest benefit shown in one of the two adult phase 3 studies (Study C1056) was mainly driven by the effect on a highly sensitive score (SELENA-SLEDAI) of disease activity, with a questionable dose-response effect and, more importantly, without a clear clinical translation on more straightforward interpretable variables (PGA, BILAG). In the subgroup of patients with positive anti dsDNA antibodies and low complement, however, the magnitude of effect was more pronounced. The data on maintenance of effect was also more convincing in these subgroups. This led to a narrowing of the indication to subjects “with a high degree of disease activity (e.g

positive anti dsDNA and low complement)". This high degree of disease activity is only defined by laboratory parameters, and that subjects with severe organ- or life-threathening disease where there is a great unmet medical need are not eligible for treatment with Benlysta, but rather subjects with a mild form of disease, usually presenting with symptoms from skin and joints.

Apart from the medical need in patients with organ- or life-threatening disease, there is a need for corticoid steroid-sparing agents in children, also in those with a more limited disease. In the phase 3 studies submitted at the time of the initial marketing authorisation for Benlysta, the effect on disease activity was accompanied by a modest corticosteroid sparing effect. There was no steroid-sparing effect found for belimumab in this paediatric study.

Compared with individuals with adult-onset disease, children with SLE have more commonly multiorgan disease, acute disease onset and ongoing active inflammation over time. SLE with childhood onset is also more often associated to rare complement mutations with an increased susceptibility to infections. In study BEL114055, there were only 13 subjects aged 6-11 years, out of which 10 were treated with Benlysta. The disease characteristics of the children included in the clinical trial were similar to the adults included in the studies from which efficacy is to be extrapolated and the magnitude of the effect was also similar.

No new safety signals were observed in the paediatric population 12 years of age and above (n=43). Safety data in children younger than 12 years of age (n=10) are limited.

A more favourable safety profile for Benlysta than for placebo was seen in the study in children, although these data are limited.

There are no important differences in the observed safety data between children aged 5-11 years and children aged 12 and above. However, the data are limited in the 5-11 years group. At the CHMP request, the MAH has strengthen the wording in the SmPC to indicate that the mechanism of action of belimumab could increase the risk for the development of infections in children with lupus, including opportunistic infections, and that younger children may be at increased risk.

Considering the risk of infections with Benlysta, the MAH committed at the CHMP request to review the possibility to undertake a PASS within established registries, to further characterise the safety of Benlysta in children with SLE, with particular focus on infections. If such a study is considered feasible, then the PASS is to be included in the RMP as a category 3 commitment.

3.7.2. Balance of benefits and risks

In summary, although SLE in small children is considered to have some different ethiopathogenesis and clinical course compared to adult and adolescent SLE, the extension of indication of Benlysta to paediatric patients is considered approvable for the following reasons:

- The extrapolation is mainly based on PK data, showing a similar exposure in children as in adults.
- The limited clinical data available indicate similar efficacy in children as in adults. Taking all available data together there is sufficient data in support of efficacy also in the smallest children.
- A more favourable safety profile for Benlysta than for placebo was seen in the study in children, although these data are limited. However, experience from adults show increased risk for infections, and there is an ongoing discussion, based on adult data, that Benlysta adversely affects the clinical course of an infection e.g. enhancing the risk for mortality due to infection. This is a main safety concern in children, and particularly for the youngest, in whom the SLE disease characteristics may make them even more susceptible compared to adolescents and adults.

- The safety of Benlysta treatment in children will be carefully monitored post-approval as described in the RMP.
- The MAH has strenghted the SmPC to further emphasise the concern of an increased susceptibility to infections in the paediatric population.

The described similarity of belimumab PK in adults and children supports the proposed posology and the extrapolation of the efficacy and safety results for Benlysta in adults to the paediatric population aged 5 to 17 years.

3.8. Conclusions

The overall B/R of Benlysta is positive as add-on therapy in children aged 5 years and older with active, autoantibody- positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti dsDNA and low complement) despite standard therapy.

4. Recommendations

Outcome

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

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

Extension of indication to include patients aged 5 years and older in the current approved indication for Benlysta (belimumab powder for solution for infusion 120 mg/ml and 400 mg/ml) based on the results of the safety, efficacy and pharmacokinetics study in patients aged 5 years to 17 years (BEL114055). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated with safety and efficacy information.

Update of sections 4.2, 4.4, 5.1, 5.2 and 6.4 of the SmPC for Benlysta (belimumab, solution for injection in pre-filled pen and pre-filled syringe, 200 mg) to reflect the paediatric data available for the intravenous formulation.

The Annex IIIA and the Package Leaflet is updated accordingly.

The RMP version 35.0 has been submitted to support this new indication.

In addition, the MAH took the opportunity to make some editorial changes in the product information and bring it in line with the latest QRD template version 10.0.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for

under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0183/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

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

Scope

Extension of indication to include patients aged 5 years and older in the current approved indication for Benlysta (belimumab powder for solution for infusion 120 mg/ml and 400 mg/ml) based on the results of the safety, efficacy and pharmacokinetics study in patients aged 5 years to 17 years (BEL114055). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated with safety and efficacy information.

Update of sections 4.2, 4.4, 5.1, 5.2 and 6.4 of the SmPC for Benlysta (belimumab, solution for injection in pre-filled pen and pre-filled syringe, 200 mg) to reflect the paediatric data available for the intravenous formulation.

The Annex IIIA and the Package Leaflet is updated accordingly.

The RMP version 35.0 has been submitted to support this new indication.

In addition, the MAH took the opportunity to make some editorial changes in the product information and bring it in line with the latest QRD template version 10.0.

Summary

Please refer to the Scientific Discussion (EMEA/H/C/002015/II/0062).