14 September 2017
EMA/CHMP/346577/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Benlysta

International non-proprietary name: belimumab

Procedure No. EMEA/H/C/002015/X/0046/G

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

BD	Becton Dickinson
BDS	Bulk Drug Substance
CPV	Continued Process Verification
CQA	Critical Quality Attributes
CPPs	Critical Process Parameters
DQ	Design Qualification
DP	Drug Product
FMEA	Failure Mode Effect Analysis
IE-HPLC	Ion Exchange Chromatography
IV	Intravenous
IPC	In-process controls
IQ	Installation Qualification
LDS-CGE	LDS-Capillary Gel Electrophoresis
LoD	Limit of detection
LoQ	Limit of qualification
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
OQ	Operational qualification
PAR	Proven Acceptable Range
PDE	Permitted daily Dose
PhEur	European Pharmacopeia
PPQ	Process performance qualification
QTPP	quality target product profile
RP-HPLC	Reversed Phase Chromatography
SEC-HPLC	Size Exclusion Chromatography
SLE	systemic lupus erythematosus
SC	Sub cutaneous
TOCS	Control of Time Out of Cold Storage

1. Background information on the procedure

1.1. Submission of the dossier

Glaxo Group Ltd submitted on 22 September 2016 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC as a consequence of the data package submitted to support the new proposed solution for injection subcutaneous presentations. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0 and to introduce some editorial changes.

The MAH applied for addition of a new pharmaceutical form (solution for injection), a new strength (200 mg) and a new route of administration (subcutaneous use).

The MAH applied for the following indication for Benlysta 200 mg solution for injection (Syringes and syringes in prefilled pen):

Benlysta is indicated as add-on therapy in adult patients 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 legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

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

At the time of submission of the application, the PIP P/0183/2016 was not yet completed as some measures were deferred.

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 received Scientific Advice from the CHMP on 21 July 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

- The application was received by the EMA on 22 September 2016.
- The procedure started on 27 October 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 January 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 23 January 2017.
- During the meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 23 February 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 20 April 2017.
- In cases when a pre-authorisation inspection has been conducted, please reflect the following steps (include/delete information as applicable):
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 24 May 2017.
- During the PRAC meeting on 9 June 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 June 2017, the CHMP agreed on a list of outstanding issues to be sent to the MAH.
- The MAH submitted the responses to the CHMP List of Outstanding Issues on 15 August 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 30 August 2017.
- During the meeting on 11-14 September 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for a group of extensions of the marketing authorisation and a variation for Benlysta on 14 September 2017.

2. Scientific discussion

2.1. Problem statement

This application is a line extension concerning the development of a subcutaneous (SC) formulation of belimumab for weekly fixed-dose administration. The recommended dosage of belimumab is 200 mg once weekly given as a subcutaneous injection in the abdomen or thigh.

The proposed indication is add-on therapy in adult patients 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 same indication as that already approved for IV use of belimumab.

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with a broad spectrum of clinical presentations encompassing almost all organs and tissues. Women are affected 9 times more frequently than men. Sixty five percent of patients with SLE have disease onset between the ages of 16 and 55 years. SLE is a chronic disease of variable severity with a waxing and waning course with significant morbidity that can be fatal in some patients. SLE is characterized by the presence of elevated levels of autoantibodies, which directly damage the body's cells and tissues or form immune complexes which cause inflammation and tissue damage.

About the product

Belimumab is a monoclonal antibody that binds to soluble human B-lymphocyte stimulator (BLyS) thereby blocking the binding of soluble BLyS to its receptors on B cells. 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.

Marketing authorization for Benlysta in the European Union was first obtained on 13 July 2011.

Benlysta is currently approved for the following indication:

Add-on therapy in adult patients 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 current authorised presentation is a dry powder for concentrate for solution for infusion with the dosing regimen of 10 mg/kg by intravenous (IV) infusion over 1 hour every 2 weeks for 3 doses and then every 4 weeks thereafter.

The proposed commercial formulation is a 200 mg/mL, ready-to-use solution for injection which supports a single 1 mL injection once weekly into either the thigh or the abdomen.

The SC administration would allow greater flexibility for patients and may offer an alternative for those with poor venous access. To this end a new formulation of belimumab has been developed which enables SC administration utilizing either a single-use disposable prefilled pen (autoinjector) or a prefilled syringe with a needle guard.

The MAH proposes to market both the SC and IV formulation concurrently.

Type of Application and aspects on development

This application concerns a grouped submission containing:

- A line extension to register new pharmaceutical form, new route of administration and new strength/potency.

The extension application is for a new solution for injection to be administered subcutaneously. The solution for injection will be presented in both a pre-filled syringe and a prefilled pen:

-Benlysta 200 mg solution for injection in pre-filled syringe

-Benlysta 200 mg solution for injection in pre-filled pen

- A Type II variation, category C.1.4, to reflect the new data submitted for the line extension in the Product Information for the currently authorised presentations.
- Legal basis

A centralised procedure according to Regulation (EC) No 726/2004, concerning Marketing Authorisation and application for a change to existing Market Authorisation leading to an extension as referred to in Annex I of regulations (EC) NO 1234/2008, or any national legislation, where applicable.

Central scientific advice was issued by CHMP on 21 July 2011 (EMEA/H/SA/717/3/2011/III).

CHMP agreed that the completed IV and SC toxicology studies (including completed SC local tolerance and SC immunogenicity studies) and the other non-clinical studies already conducted were adequate to support the Phase 3 SC study and filing of the Biologic License Application (BLA)/line extension.

Agreement was reached on the proposed population PK analysis using a nonlinear mixed effect modeling approach based on a pooled PK dataset.

CHMP also agreed that, in principle, positive results from a single Phase 3 pivotal study of similar design to the prior pivotal IV studies should be adequate to support the filing for the new formulation and route of administration, considering also that the company was targeting a similar overall exposure with the SC formulation as compared to the approved 10 mg/kg IV dose. A placebo controlled study was accepted. Other key design aspects of the pivotal Phase 3 study were discussed including eligibility criteria, sample size, background medication, primary and major secondary endpoints, statistical analysis approach, and proposed adverse events of special interest (AESI).

2.2. Quality aspects

2.2.1. Introduction

Benlysta (Belimumab) is a recombinant, human IgG1λ monoclonal antibody that binds and antagonizes the biological activity of soluble B lymphocyte stimulator (BLyS) protein, a member of the tumor necrosis factor (TNF) ligand superfamily that promotes the survival of B lymphocytes. Belimumab was developed for the treatment of patients with systemic lupus erythematosus (SLE). The currently approved presentations are a powder for concentrate for solution for infusion, 120 mg/vial and 400 mg/vial.

With this extension application the applicant proposes a new pharmaceutical form, solution for injection, to be administered subcutaneously. Two presentations are applied for: 200 mg solution for injection in prefilled syringe with needle safety device and 200 mg solution in prefilled pen (auto-injector).

2.2.2. Active Substance

General Information

Belimumab is produced in a NS0 cell line using a production medium. The purification process comprises a series of chromatographic steps, viral inactivation and filtration steps, and formulation. The purified bulk active substance (BDS) is filled in storage containers and shipped to the finished product manufacturing site.

The M18 process is the BDS process for the clinical SC finished product, while the M21 process is the BDS process for the commercial SC product.

Manufacture, characterisation and process controls

Manufacture and process controls

The listed manufacturers and testing sites have been qualified to perform manufacturing, storage and control of active substance in compliance with GMP.

(step 19). The manufacturing process of these steps and process controls are at large acceptably described. The lifetimes of the filtration cassettes have however not yet been defined and reference is given to an ongoing validation study. However, interim effective lifetime for the commercial purification process is based on current data. Full results from this study will be provided upon completion of the study (Recommendation). Furthermore, in the meantime, in-process controls (IPCs) for integrity, water permeability as well as microbiological controls are in place.

Reprocessing may be performed of the bulk filtration material in case of failure of the post-use filter integrity test or other mechanical failures. This has been validated in small-scale studies. Such reprocessing will be performed according to written procedures and a step-specific production batch record, and the first reprocessed lot will be monitored according to cGMP stability protocol. This approach is considered acceptable.

Control of critical steps and intermediates

For the M21 process acceptable information has in general been provided. Together with the control of process parameters listed in section S.2.2 the control strategy is found acceptable. The control strategy is further discussed below.

The IPC test methods have either been validated or qualified. The IPC test methods (have been described For each step, action and alert limits have been set for bioburden and endotoxin. These limits are based on historical data and process capability. will be established after a minimum of commercial scale runs and will be used to monitor process performance.

Process validation

For the M21 process, the Phenyl SFF pool is concentrated and diafiltrated into a new formulation buffer during the UF/DF step (Step 16). A Single Pass TFF step (Step 17) was introduced to the process following the UF/DF step for further concentration of the product. A summary of changes from the M15 to M21 process has been provided.

The process validation as well as process characterisation has been summarised. For the process characterisation of the steps a design of experiments (DoE) approach was used. No details from the DoE and process characterisation are provided, but it is claimed that all data is available for inspection. However, the process parameters defined as critical and key for the M21 process, including the operating ranges, are listed. Examples or summaries from the DoE and process characterisation had been useful for the support of the proposed control strategy. The proposed control strategy for the concerned steps which primarily only covers concentration and formulation, appears adequate. Furthermore, the summarised data provided from the validation studies (supporting studies for downstream process validation and conformance lots) are found supporting for the conclusion that adequate controls are in place.

BDS batch release results for three conformance lots as well as the one supportive lot are provided. All batches comply with the acceptance criteria and demonstrate satisfactory consistency in batch results. The deviations occurred in relation to in-process results (feed pressure and flow rate which were claimed to be set too tight based on laboratory scale, two in-process bioburden results above action limit for chromatography step, endotoxin level above alert limit which was related to slightly elevated level in the WFI) have been acceptably described and justified. Relevant corrective and preventive

actions have been implemented. For all downstream data from analyses of the conformance lots reference is given to a validation report not provided. However, considering the summarised results provided from downstream validation and transport validation together with the batch results from the conformance batches, the data provided is in general found sufficient to verify satisfactory performance and consistency of the manufacture.

However, as discussed above the lifetimes of the cassettes have not yet been defined with reference is to the ongoing validation study.

Manufacturing process development

The process development of the BDS SC manufacturing processes has been satisfactorily described. M21 is the proposed commercial process for liquid product intended for SC administration. Two formulations have been used during the development, and the proposed commercial formulation, is the same as that used in the Phase 3 clinical studies. M16 has been used in Phase I studies and M18 in Phase II and III. The main change between the M18 and M21 process is the addition of, after the step. The formulation is the same although the diafiltration buffer and polysorbate stock solution was modified.

Three comparability assessments have been performed which by large is found acceptable. In the third study three BDS batches of M18 and three batches of M21 was compared. In these three studies side by side testing has been performed using relevant test attributes covering analytical release methods and additional characterisation studies such as oxidation, size variants and deamidation. By large the data is comparable for the M18 and M21 process except for slightly lower main peak and higher acidic peaks in the M21 process BDS lots. The root cause and acceptable correction actions were taken.

Although the approach using the specification limits as acceptance criteria for the comparability studies cannot be fully supported considering the quite wide acceptance criteria, the batch data from the side-by-side comparison at such is however found acceptable. The results demonstrate that the change in process from M18 used in phase 3 clinical trials to the M21 commercial BDS does not have any significant effect on the quality or analytical profile of BDS material.

Characterisation

Acceptable information about the characterisation of belimumab has been provided. For the complete data on characterisation of belimumab reference is given to the dossier for the currently licensed lyophilised IV products. To elucidate structures and properties of belimumab potentially affected by the liquid formulation and the effects of the different pH and excipients, a subset of the characterisation tests have been repeated. Acceptable information from these studies as well as from the comparability studies has been provided to verify that the primary structure and high order structure of belimumab liquid product in formulation 06-D are comparable and highly similar to the belimumab lyophilised product in formulation 06-B.

It is agreed that no major differences in process-related impurities and product-related variants are expected between the product in liquid formulation and the product in lyophilisation formulation due to the similarity of the manufacturing processes. Nevertheless, some of the process related impurities such as small molecules (downstream process) and extractables/leachables have been adequately reassessed due to changes in process equipment and formulation.

Charge variants have been previously characterized in belimumab BDS in lyophilised formulation 06-B and no new charge variants were detected in liquid product in formulation 06-D at release or upon recommended storage. This is also discussed in section S.2.6. where comprehensive data comparing batches from M16, M18 and M21 are provided.

Taken all information together the characterisation of the active substance is found sufficiently addressed.

Specification

Relevant tests are included in the specification for the active substance. The specifications for belimumab BDS were established and justified based on acceptance criteria and experience from the belimumab IV BDS process (M15) and from experience with the subcutaneous BDS processes (M18 and M21). The acceptance criteria for pH, osmolality and protein concentration were changed due to the changed formulation. Nevertheless, in response to a question the applicant proposed to keep the shelf life limit for and slightly tighten the release limit. The shelf life was also decreased.

For the calculation of the acceptance criteria for an approach using a worst case lot was used. Also the relationship between levels of in aged active substance batches (based on stability data) and finished product at release was evaluated.

Although data is limited the available data indicate that the acceptance criteria for active substance will assure compliance with the finished product release criteria.

Altogether with the limitation of data presented the applicant is recommended to put active substance batches with levels close to the release limit on stability studies to conclude about the stability trend at such higher levels. An action limit for what level of should trigger such a stability study should be defined. The proposed acceptance limits for on active substance can be accepted with this recommendation.

For most analytical methods reference is given to compendial methods or The following methods have been slightly modified: appearance, identity, protein concentration, purity, charge heterogeneity, residual DNA, host cell protein. For the modified methods a summary of the differences are included in this section. Although a clear reference to the dossier for the IV product is given for the modified methods as well as good summaries of the differences, full descriptions relevant for the SC product were requested during the procedure. The dossier was updated as requested with the applicant's responses.

The applicant was asked to update the specification and test method with a unique identification number for each test method which assures a clear link between specification, test method and method validation. In their responses, such unique identification numbers were included in the specification, method descriptions and validation documents.

Partial or full validation has been performed on the test methods except for the compendial methods where a qualification study was performed. The validation approach used as well as the validation results is found acceptable to justify the suitability for the intended purpose.

Batch data has been provided for both non-clinical and clinical batches, as well as three batches of belimumab BDS manufactured by the commercial M21 process. By large the batch data demonstrate consistency although slightly higher values for total acidic peaks can be observed for the M21 process compared to M18 and M16, although still within the acceptance criteria. This has been further discussed above. The process change from M15 to M18/M21 is claimed not to impact the attribute for potency and thus the criteria applied to the M21 BDS is the same as that established for the approved IV product (M15 process).

Stability

A shelf life of 48 months was initially proposed for M21 belimumab BDS at the intended storage condition of -40ºC protected from light. In the response to the Day 180 LoQ the applicant proposed to decrease the shelf life from 48 months to 36 months.

Three batches belimumab BDS from the M18 and M21 manufacturing process respectively, in the commercial formulation buffer 06-D, have been included in the stability program.

To justify the proposed shelf life and storage conditions, 36 months stability data (-40 ºC) has been provided for three batches manufactured according to the M21 process. In addition supportive data from three batches of the M18 process have been provided (60 or 48 months). The studies are on-going. Also data from accelerated studies at -20°C and 2-8°C stability data are provided. The data indicates that the stability profile for the M18 and M21 process is comparable and the data from M18 can be supportive. For all batches a slight increase can be observed at the proposed storage condition although still within acceptance criteria. At the accelerated condition at -20°C a significant increase could be observed and the results for purity were out of acceptance criteria after 6 months for both M18 and M21 process. However, it is noted that the acceptance criteria was with margin applied to when stored at 2-8°C.

Based on the full time data for the M18 batches and the available 36 months for the M21 batches, the claimed shelf life of 36 months when stored at -40ºC protected from light, is found approvable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Belimumab 200 mg solution for injection is supplied as a single-use, sterile liquid finished product in two formats for subcutaneous use. The formats include a prefilled syringe assembled with additional functional components to create a prefilled auto-injector, referred to as belimumab finished product in auto-injector, and a prefilled syringe assembled with additional functional components to create a safety syringe device, referred to as belimumab DP in safety syringe. Both device formats use the same prefilled syringe container closure and contain 200 mg of belimumab for SC use.

Table 2 - Complete composition of Benlysta, solution for injection

Ingredient	Reference	Amount (mg/ml)	Function
Belimumab	In-house	200	Active
Sodium Chloride	PhEur	6.7	Stabilizer / Tonicity Modifier
L-Arginine Hydrochloride	PhEur	5.3	Stabilizer
L-Histidine Monohydrochloride	PhEur	1.2	pH buffer
L-Histidine	PhEur	0.65	pH buffer
Polysorbate 80	PhEur	0.1	Surfactant
Water for injection	PhEur	q.s. to volume	

Figure 3 - External Appearance of the Belimumab Finished product in Prefilled Pen (Auto-injector-Before Use)

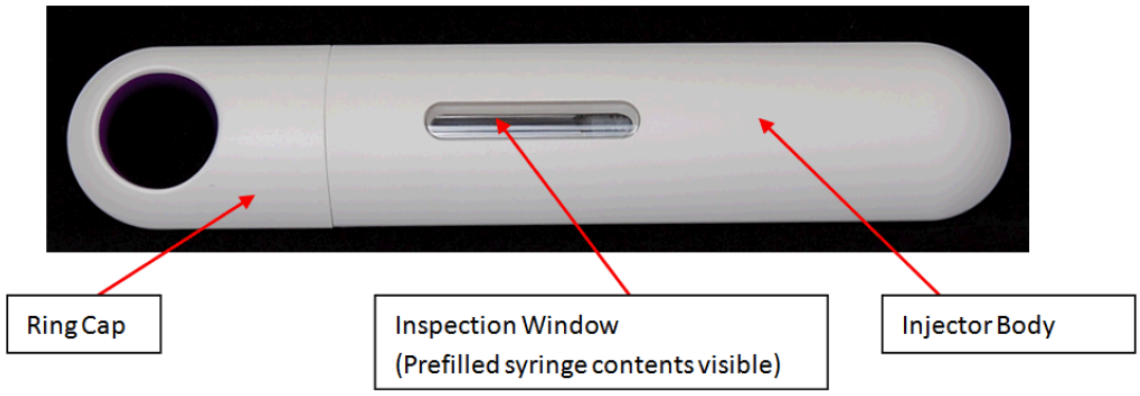
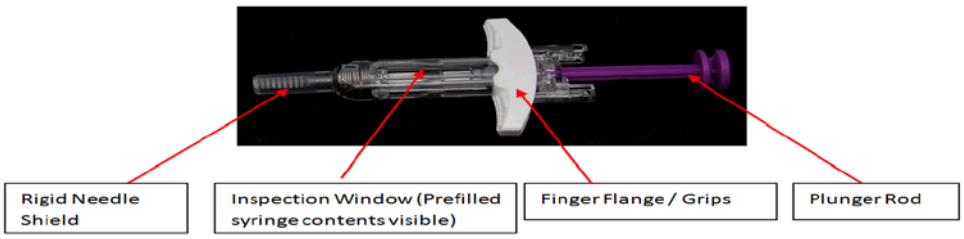


Figure 4 - External Appearance of the Belimumab finished product in Safety Syringe (After Use)



The finished product does not have an overage. It is manufactured with an excess volume to ensure a deliverable volume of 1.0 mL.

The belimumab BDS concentrated formulated bulk solution is containing the same excipient components and excipient concentrations as the finished product. During the course of development of belimumab for subcutaneous administration, two formulations were used (). The proposed commercial formulation is the same as that used in the Phase 3 clinical study. The extensive formulation development has been satisfactorily addressed.

Also an extensive manufacturing process development has been performed. Process characterisation studies were performed on each unit operation to conclude about risk and criticality of process parameters, and from this knowledge define proven acceptable ranges. The process characterisation studies performed on each unit operation has been summarised and the outcome adequately discussed. For example the filter membrane steps have been investigated with regards to pressure, multiple filtrations, filtration time, protein adsorption, flow rate. Refiltering of the bulk finished product can be performed in the. For justification of this re-processing reference is given to development studies as well as re-processing of two GMP clinical trial batches which were placed on stability studies. No impact on quality or stability was observed. Reprocessing in the context of is found acceptably justified.

The risk assessment and control strategy development are found acceptably described although no details or examples from the failure modes and effects analysis (FMEA) were given. However, the critical quality attributes (CQA) have been defined and the relationship to the quality target product profile (QTPP) clearly indicated. A comprehensive summary table of critical process parameters (CPP) and IPC as well as justification relative to CQAs are provided. Furthermore, the pharmaceutical

development studies and other data used in characterizing unit operations of the finished product manufacturing process have been satisfactorily summarised and discussed. The chosen control strategy is found adequate and acceptably justified.

Also the development of the devices (auto-injector or safety syringe) and the assembly process including the control strategy has been adequately addressed. The defined CQAs and CPPs for the assembled auto-injector and the safety syringe are listed as well as the rationale for the classification.

The auto-injector was not included in the Phase 3 study. Clinical bridging studies were performed which are further discussed in the Pharmacokinetic and the Clinical AR respectively. It is claimed that the primary difference between the clinical assembly machine and the commercial assembly machine is that the commercial assembly machine includes more extensive in-process controls and monitoring systems for the assembly steps. It is found acceptably justified that the two assembly processes produce equivalent devices.

Furthermore, the suitability of the primary packaging has been assessed. The functionality of both the auto-injector and safety syringe has been studied.

The development of the auto-injector and the selection of the related components for the safety syringe using human factors studies have been satisfactorily described. Details regarding these formative human factors studies leading to the device selection are provided in the human factors validation report (Section 3.2.R).These studies are assessed in the clinical assessment report.

The strategy with respect to microbiological quality assurance of the finished product is adequately addressed and found acceptable. The product container closure system has been validated and stability studies include container closure integrity testing.

Finally, this section includes information about studies used to assess the compatibility of the product in its container closure during various storage and in-use conditions. It has been demonstrated that the quality and stability of finished product is not impacted by stress associated with shipping and physical dropping of the device.

Manufacture of the product and process controls

Manufacture of the finished product, primary and secondary packaging, quality control testing and batch release take place at Glaxo Operations UK Ltd, Harmire Road, Barnard Castle, County Durham, UK.

Manufacture of finished product

Reprocessing of may be performed This is found acceptably justified by the small-scale development study as well as results from reprocessing of two GMP clinical batches.

The description of the manufacturing process and information of in-process controls for the manufacture of the final finished product is given in sufficient detail..

Controls of critical steps and intermediates

Critical process parameters and in-process controls with justification relative to CQAs, and method of control for belimumab finished product manufacture were provided. Critical in-process controls were determined based on product and process understanding and utilization of risk management principles to ensure product quality. The manufacturing process is controlled throughout production using a combination of in-process performance tests, critical in-process control tests and defined operational ranges for process parameters.

With the additional information provided in the applicant's responses the information about the CPP and IPC is considered sufficient. Relevant controls are in place to assure satisfactory process performance and finished product quality. The link to the defined CQAs was satisfactorily addressed in the section for manufacturing process development. The control strategy for the commercial finished product manufacturing process was developed by a combination of process characterisation studies, clinical manufacturing experience, process performance qualification (PPQ), and risk assessment. The process characterisation studies and manufacturing experience facilitated risk analysis and identification of critical process parameters during the risk assessment exercises. CQAs were identified for the product and FMEA was also performed for each process parameter. The chosen control strategy is found adequate and acceptably justified.

Process validation

A three-stage approach (stage 1: process design; stage-2: process qualification; stage-3: continued process verification) was used for the process validation. An adequate development work was performed in stage 1 where extensive process characterisation studies were performed on each unit operation to conclude about the impact on the CQAs. The data from the process performance qualification demonstrates a well-controlled process where all results complied well with acceptance criteria. Hold time has been satisfactorily addressed both from a stability and microbiological (media fills) point of view. Compatibility with the holding bag was acceptably demonstrated.

Also acceptable compatibility of the sterile filter has been studied as well as microbial retention. The maximum time given for the sterile filtration and filling step is acceptably justified. Media fill validation of the line filling was performed. No contamination was observed.

Finally, the device assembly has been appropriately validated by the process qualification process.

Product specification

Release and shelf-life specifications are in place for the unassembled pre-filled syringe. In addition the assembled devices have a separate set of specifications and acceptance criteria to ensure functionality of the devices. This approach is found acceptably justified by the development studies demonstrating that the assembly of the prefilled syringe into devices does not impact finished product quality of the prefilled syringe.

The specification covers appropriate parameters which are in good agreement with the specification approved for the licensed lyophilised product where relevant.

The strategy for setting the specifications is in line with ICH Q6B and takes into account data from batches used in clinical trials, manufacturing experience, analytical method performance and stability data. The applicant also claims that indication, dose and dosage frequency, PK/clearance, clinical efficacy and safety have been taken into account.

The main principle for the establishment of acceptance criteria is considered acceptable. However, a statistical evaluation of the prefilled syringe release data was performed and the range calculated was presented. This is found acceptable from process and analytical capability point of view although some acceptance criteria of relevance for the safety and efficacy should be within the range of clinical experience.

In their responses the applicant proposed to tighten the shelf life limit for aggregates to align with the IV product specifications and also agreed to tighten the finished product release limit. The relevance of the data from the IV administration as justification for accepting wider limits for purity by SEC-HPLC than are justified by the batch/stability and clinical data generated for the SC formulation were not

found conclusive. There is a known risk of hypersensitivity reactions with the IV product and the SC product is intended for unsupervised self-administration by patients at home (with no premedication). Thus, the setting of administration of the product is not comparable. In addition, literature articles cite that more frequent dosing e.g. a subcutaneous route of administration rather than an IV route might facilitate the ability of small amounts of aggregates to enhance immune response (Rosenberg 2006). Further, it is not within the scope of this assessment to extrapolate from data in the literature for other products such as trastuzumab (Hillenbach 2015). Therefore, it was considered that the shelf life limit for aggregates remained to be tightened in line with batch/stability data to a limit which can be justified as clinical safe based on clinical experience with the SC product. The release limits for finished product and active substance were also requested to be revised as appropriate.

With their response, the applicant proposed to further tighten the shelf life limit for aggregates in finished product. For the calculation of the revised acceptance criteria for aggregates on finished product a worst case lot was used for the modelling. The approach used was found reasonable and has been agreed to.

As part of the response, the applicant also provided clinical information on systemic and local site reactions observed during the SC trial. These reactions have previously been assessed in earlier rounds of this procedure. It is agreed that within the clinical study BEL112341, the incidences of hypersensitivity reactions and/or post-injection systemic reactions were low in both treatment groups, with lower or similar reported frequency in the belimumab 200 mg SC group as compared to placebo group. It is also agreed that all reported local injection site reactions were mild or moderate in severity. However, given also the identified risk of systemic hypersensitivity reactions with the IV product and the at-home setting of administration of the SC product, the acceptance of wider limits than justified by the batch/stability and clinical data generated for the SC formulation was not supported. The revised limits now more closely reflect the range of experience in the SC trial. This can be accepted. From a clinical perspective, this issue i.e. the reporting of systemic and local reactions by product will also be further followed in future PSUR submissions.

In conclusion, the revised acceptance criteria for aggregate on finished product are found approvable.

However, the limits are set wider than fully supported by batch and stability data. The limits are also wider than levels in batches of the SC product used in clinical trials and the applicant was at day 120 asked to tighten the limits to mirror process consistency and further justify the conclusion about non-significance of deamidated forms in batches at higher levels than used in clinical trials.

In the applicant's responses the limits for charge heterogeneity were slightly tightened based on a recalculation of previous available batch results from M18 and M21 process plus three 3 additional batches that were not available in the initial analysis. the proposed revised release are found acceptable to assure satisfactory consistency.

Also the shelf life limits have been slightly tightened

The applicant has provided an extensive discussion about the deamidation of belimumab and concludes that the results indicate that deamidation occurs rapidly upon injection with no apparent impact on clearance, safety or efficacy.

This conclusion is found reasonable and the proposed revised shelf life limits for charge heterogeneity is found acceptably justified.

Analytical methods

For most test methods the same methods are used for both BDS and finished product. For compendial methods reference to Ph. Eur. is given. In addition summaries of the methods were provided for

appearance, sterility, bacterial endotoxins. Briefly summarised method descriptions have also been provided for the in-house methods for delivered volume, injection forces, delivered volume, auto-injector needle guard lockout and safety syringe actuation and needle guard location. These are found acceptable.

Since most test methods are the same for both BDS and finished product, the method validation and qualification reports cover both BDS and finished product and are addressed above for the BDS. For the test methods that are only used for finished product, summaries of validation and qualification studies have been provided. Also summaries of the validation studies of the additional device-specific tests are provided in this section. The information provided related to validation of the methods only used for the finished product is found satisfactory to verify the suitability and acceptable performance of the methods. The validation was performed according to ICH guidelines where relevant. For the test for delivered volume and injection force also compliance with the requirements by ISO-11608-1 (e.g. Gauge Repeatability and Reproducibility) was verified.

Container closure system

The container closure system for belimumab 200 mg solution for injection is composed of a prefilled syringe (PFS) as the primary container closure which is assembled into a prefilled pen (auto-injector) or a safety syringe device. The syringes and stoppers meet Ph. Eur. requirements for Type I glass. The needle shield insert is a proprietary formulation qualified to meet ISO 10993-1 (Biological Evaluation of Medical Devices).

An overview of the design and operation of the prefilled pen (auto-injector) and safety syringe device has been provided. A technical file on the auto-injector is provided in 3.2.R. The devices comply with the relevant requirements set forth by ISO 11608-1 and ISO 11608-5.

Stability

A shelf life of 36 months at the intended storage condition of 2-8°C, protected from light, is proposed.

Until now 24 months long-term stability data have been presented for the three first manufactured DP batches manufactured from BDS from the M21 manufacturing process. The study is on-going up to 60 months. To support the proposed shelf life of 36 months when stored at 2-8°C, protected from light, full long time data has been provided for five batches manufactured from BDS from the M18 manufacturing process, as well as supportive data from four additional batches manufactured from BDS M18. Considering that BDS derived from the M18 and M21 processes has been shown to be equivalent, as discussed above, the approach to base the justification of the shelf life on the “M18” batches is found acceptable.

In addition 6 months accelerated data are provided for all batches after storage at 25°C/60%RH and 40°C/75%RH (stressed). Also the impact of light exposure was studied.

The tests and acceptance criteria are a subset of the test included in section 3.2.P.5 although the major parts of the tests are included. The chosen quality attributes has been acceptably justified.

The data up to now demonstrates compliance with the acceptance criteria applied for batches stored at 2-8ºC and indicate similar stability behavior as for M18.

In conclusion, a comprehensive stability program has been presented and the results have been summarised and discussed in a sufficient way. The presented data supports the proposed shelf life of 36 months when stored at 2-8°C.

Adventitious agents

With regard to adventitious agents safety evaluation reference is given to the dossier for the licenced belimumab IV product (lyophilised product). This is found acceptable.

For these component contact materials, suppliers have provided assurances that, where used, any tallow-derived raw materials used in the manufacture of these components fulfil the requirements of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products EMA/410/01.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The Benlysta dossier is of good quality and no major objections were identified in the documentation submitted. The issues raised during the review have been acceptably addressed.

Active substance

The M18 process is the BDS process for the clinical SC finished product, while the M21 process is the BDS process for the commercial SC product. The manufacturing process and IPCs for the steps which are unique for the current BDS M21 process for subcutaneous use have been adequately described.

For the steps specific for the M21 process acceptable information about control of critical steps has been provided and the general control strategy presented is found acceptable.

The process development of the BDS manufacturing processes has been satisfactorily described. M21 is the proposed commercial process for liquid product intended for SC administration. Two formulations have been used during the development and the proposed commercial formulation is the same as that used in the Phase 3 clinical studies.

Process validation and evaluation data is found sufficient to support a consistent performance of the manufacturing process.

Relevant tests are included in the specification for the belimumab BDS. The specification was established and justified based on acceptance criteria and experience from the belimumab IV BDS process (M15) and from experience with the subcutaneous BDS processes (M18 and M21).The justification of the specification for the BDS is found acceptable. The stability data provided supports the proposed shelf life of 36 months when stored at -40ºC protected from light.

Finished product

The description of the manufacturing process and information of in-process controls for the manufacture of the final finished product is given in sufficient detail.

Relevant tests are included in the specification of finished product (separate specification for unassembled prefilled syringe and device functionality). The strategy for setting the specifications was in general agreed to with the exceptions for the limits proposed for purity by SEC-HPLC.. The revised limits more closely reflect the range of experience in the SC trial and are found acceptable.

Furthermore, during the procedure the applicant was also asked to tighten the limits for charge heterogeneity In the response the limits were slightly tightened based on a recalculation of data. In respect to this the applicant concluded that administration of finished product with variation in acidic content up to will have a negligible impact. This conclusion is found reasonable and the proposed shelf life limits for charge heterogeneity is found acceptably justified.

The data reported from the batch analysis demonstrates acceptable consistency in production.

A shelf life of 36 months at the intended storage condition of 2-8°C, protected from light, is proposed. Until now 24 months long-term stability data have been presented for the three first finished product batches manufactured from BDS from the M21 manufacturing process. To support the proposed shelf life, full long time data has been provided for five finished product batches manufactured from BDS from the M18 manufacturing process, as well as supportive data from four additional batches manufactured from BDS M18. Considering that BDS derived from the M18 and M21 processes has been shown to be equivalent the approach to base the justification of the shelf life on the "M18" batches is found acceptable. The proposed shelf life of 36 months when stored at 2-8°C is acceptably justified by data.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product applied for by this line extension is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommended several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

This is a line extension of Benlysta to propose a new commercial formulation 200mg/ml which enables sc administration, ready-to-use solution for injection which supports a single 1 mL injection once weekly into either the thigh or the abdomen. This proposed fixed 200 mg SC dose targets a similar belimumab exposure in terms of average steady-state AUC as the monthly 10 mg/kg IV dosing approved in SLE patients.

Since the initial IV application 3 additional primary pharmacology studies have been conducted to investigate potential binding of belimumab to TNF family members and Fc-mediated functions of belimumab.

Secondary pharmacodynamics studies, safety pharmacology studies and pharmacodynamics drug interaction studies were not performed related to the present line extension application.

Regarding pharmacokinetics, additional studies were conducted in mice to investigate the pharmacokinetic comparability between a reference belimumab liquid formulation and an aged belimumab liquid sample as well as to determine the pharmacokinetics of a deamidated belimumab isolate and to evaluate the toxicokinetics in monkeys following subcutaneous administration.

An in vitro study has also been performed to investigate the metabolic fate of belimumab.

Neither in the initial IV application nor in the present distribution or excretion studies were performed.

Non-clinical in vivo studies weren't performed to investigate potential pharmacokinetic drug interactions with drugs that are likely to be co-administered with belimumab in the clinic.

Regarding toxicology, since the approval of the IV application only an 8-week local tolerance study was conducted to evaluate the potential for irritancy of belimumab, when administered 3 times via subcutaneous injection to cynomolgus monkeys over 29 days (3 total doses) and to assess the reversibility of persistence of any effects after an additional 4 weeks.

2.3.2. Pharmacology

Since the initial IV application 3 additional primary pharmacology studies have been conducted to investigate potential binding of belimumab to TNF family members and Fc-mediated functions of belimumab.

The results demonstrated that belimumab has affinity to BLyS, but not to the other related TNF members investigated (APRIL, TNFα, TNF-β, LIGHT, FasL or TL1-A). Competition experiments showed that BLyS binding to immobilized belimumab was inhibited in the presence of increasing concentrations of belimumab. In these competition experiments IC50 values of 0.9 and 1.3 nM on the high and low density surfaces was obtained respectively, which is 3-4 fold higher than the previously reported affinity of belimumab for BLyS which is about 0.3 nM. The Applicant states that the higher IC50 values obtained in the competition experiments may be due to differences in reagent lot concentrations/potency.

Analyses of BIAcore sensorgrams demonstrated that the Fc region of belimumab (human monoclonal anti-BLys IgG1) binds to FcRn with a Kd comparable to raxibacumab (human monoclonal anti-protective antigen IgG1) and rituximab (human monoclonal anti-CD20 IgG1). Viability was similar between human IgG1, rituximab and belimumab treated BLyS expressing monocytic U937 cells. This is consistent with the lack of CD20 expression on the surface of U937 cells and therefore lack of rituximab-mediated ADCC.

In B lymphocytic ST486 cells expressing CD20, rituximab induced killing was inhibited in the presence of an anti-idiotypic antibody to rituximab. Belimumab, both in the presence and absence of BLyS did not affect the viability of the cells compared to the isotype control. This result is consistent with the mechanism of action of belimumab not resulting in ADCC of B cells.

Compared to the untreated controls and to the matched human IgG1 control, no reduction in viability was observed in BLyS-expressing U937 cells in the presence of belimumab and 10% human serum. In contrast, CD20 expressing ST486 cells were efficiently killed (> 99%) in the presence of rituximab (anti-CD20) and 10% human serum. The viability of ST486 was similar to untreated controls or human IgG1 isotype control when heat-inactivated serum (in which the complements are inactivated) was used with rituximab. This result is consistent with the mechanism of action of belimumab not resulting in CDC mediated killing of BLyS-expressing cells.

An equilibrium binding method was used to determine equilibrium constants (Kd) of belimumab and various control antibodies to human FcγRIIIa. The measured Kd values for belimumab, rituximab and IgG κ were 1.79, 2.09 and 2.68 µM, respectively. IgG4 binding was too low to get an accurate measurement. These values are consistent with the ~1 µM Kd value previously reported for monomeric human immunoglobulins. The results obtained in the CDC and ADCC assays with primary human CD14+ monocytes confirm that belimumab does not mediate these effector functions while another anti-BLyS antibody, 9B6, known to bind to cell surface BLyS was able to mediate both CDC and ADCC activity, although the 9B6 mediated CDC activity was less pronounced compared to the activity observed with rituximab on the CD20-expressing cell line. The concentration of belimumab (66 nM) used for analysis of CDC and ADCC effector functions were 200 times the Kd, therefore all BLyS would

be predicted to be complexed with belimumab which would generate a maximum Fc-mediated effector response.

No secondary pharmacodynamics studies, safety pharmacology studies or pharmacodynamics drug interaction studies were performed related to the present subcutaneous injection application.

2.3.3. Pharmacokinetics

Since the initial IV application, additional pharmacokinetic studies have been conducted in mice to investigate the pharmacokinetic comparability between a reference belimumab liquid formulation and an aged belimumab liquid sample as well as to determine the pharmacokinetics of a deamidated belimumab isolate (varying deamidation levels) and to evaluate the toxicokinetics in monkeys following subcutaneous administration.

An in vitro study has also been performed to investigate the metabolic fate of belimumab.

Serum belimumab concentrations in mice and monkeys were determined by an electrochemiluminescence (ECL)-based ELISA assay. A quantitative measure of the ECL signal emitted by each well was recorded, and the ECL counts emitted by the standard calibrators were used to generate a standard curve using a 4-parameter logistic (4PL) fit. The concentrations of belimumab in the serum samples were calculated from the standard curve. The lower limit of quantitation (LLOQ) of the assay was 100 ng/mL of belimumab in 100% mouse serum. The same assay was used for the serum concentration determination of deamidated belimumab. Dosing solutions of the reference belimumab liquid formulation, aged belimumab liquid sample and deamidated belimumab were analysed using the same assay.

Immunogenicity of belimumab was evaluated using an ECL-based ELISA assay. The plate was read for ECL counts. The ratio of the sample and negative control ECL signals was compared with the cut point established using 12 BALB/c mouse serum samples (1.150). Samples that give a ratio above the screening cut point were considered potential positive.

Due to the sample volume limitation the confirmatory assay was not performed and the screening positive samples were considered confirmed positive. The bioanalytical methods are considered adequate.

Either distribution or excretion studies were not performed in the initial IV application nor in the present.

2.3.4. Toxicology

No single dose toxicity, repeat-dose toxicity, interspecies comparison, genotoxicity, carcinogenicity, reproductive and developmental toxicity or other toxicity studies were conducted in relation to the present SC administration application.

Since approval of the IV application, an 8-week local tolerance study was conducted under GLP-compliance to evaluate the potential for irritancy of belimumab, when administered 3 times via subcutaneous injection to cynomolgus monkeys over 29 days (3 total doses) and to assess the reversibility of persistence of any effects after an additional 4 weeks.

All monkeys that were given belimumab by SC administrations at the 1000 mg/dose demonstrated systemic exposure. Following SC administration of 3 doses on days 1, 15 and 29 the Cmax increased by 59% and the through serum concentration increased about 2-fold. This was expected due to the long t1/2 in the cynomolgus monkey.

2.3.5. Ecotoxicity / environmental risk assessment

Belimumab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no Environmental Risk Assessment for guselkumab is required.

2.3.6. Discussion on non-clinical aspects

The pharmacodynamic in vitro studies conducted demonstrated that belimumab binds to and antagonizes the biological activity of human soluble BLyS. The Applicant states that the higher IC50 values obtained in the competition experiments may be due to differences in reagent lot concentrations/potency, which is agreed.

The data provided in the new study reports show that the Fc portion of belimumab has affinity to both FcRn and FcγRIIIa. However, based on the results obtained the in vitro pharmacology studies there is no indication that belimumab mediates ADCC or CDC.

No secondary pharmacodynamics studies, safety pharmacology studies or pharmacodynamics drug interaction studies were performed related to the present subcutaneous injection application, which is acceptable.

Following a single 10 mg/kg SC dose of reference belimumab liquid formulation or aged belimumab liquid sample, PK of belimumab were similar and the 95% confidence interval for all PK parameters were overlapping between the two groups. For the deamidated belimumab the Tmax and Cmax values were similar to the reference belimumab liquid formulation and the aged liquid sample. As serum levels of deamidated belimumab decreased to below the LLOQ (100 ng/ml) on day 10 a comparison of other PK parameters were not possible to perform.

The MAH states that the decreased serum concentrations in the animals dosed with the deamidated belimumab correlates to a higher incidence of ADA which either increase the clearance rate of the resulting belimumab-ADA complex or mask domains critical for binding to BlyS (neutralizing antibodies) which makes belimumab undetectable in the PK assay. This is agreed. It is noted that only female mice were used in the PK study.

The results provided by the Applicant indicate that BlyS does not affect CYP1A2, CYP2C8, CYP2C9 or CYP3A4 mRNA expression in a concentration-dependent and reproducible manner in contrast to the prototypic CYP suppressors IL-6 and TNFα.

No distribution or excretion studies were performed in the initial IV application or in the present, which is acceptable.

The local tolerance study in cynomolgus monkeys did not provide any indication of belimumab-related effects in mortality, clinical observations, body weights, dermal irritation evaluations, clinical pathology and skin punch biopsy of the dose site of administration. The only effect observed was a reduction in B cells which most likely is related to the pharmacology of belimumab. Thus, belimumab administered by repeated SC injections to cynomolgus monkeys exceeding the intended human clinical SC dose 9- to 14–fold on a mg/kg basis appears to be well tolerated. It is noted that only male cynomolgus monkeys were used in the local tolerance study.

From a non-clinical point of view the results of the additional nonclinical studies do not alter the original conclusions regarding the nonclinical efficacy and safety of belimumab for IV use in patients with SLE and in addition support the SC use of belimumab under the proposed clinical dosing regimen.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers that from a non-clinical point of view this line extension for Benlysta is approvable.

2.4. Clinical aspects

2.4.1. Introduction

The Phase 1-3 clinical development program for belimumab SC in SLE is comprised of 7 studies, 5 of which utilize the current to-be-marketed formulation (06-D), and the proposed SC dose of 200 mg. The Phase 3 trial BEL112341 is pivotal for the belimumab SC formulation, supported by the belimumab IV studies (C1056 and C1057) that formed the basis of the evidence for the initial approval of IV belimumab.

The final commercial device formats (autoinjector and safety syringe) were not included in the pivotal Phase 3 trial. As part of the device bridging program for the autoinjector, a real-life use study of the autoinjector device was conducted; study 200339 was an 8-week single arm study with the objective to provide supportive data for the autoinjector for self-administration of belimumab and to further characterize the change in belimumab trough concentrations when switching from the IV to the SC administration.

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

Study Number	Study Objectives	Treatment Details (Test Product(s); Dosage Regimen; Duration of Therapy; Belimumab SC Conc [mg/mL] (Formulation)
Phase 1- Healthy Volunteers		
C1058	Phase 1 study to evaluate the absolute bioavailability, PK, and safety of a single dose of belimumab administered SC to healthy subjects	Belimumab 100 mg single dose; SC injection or IV infusion; Belimumab 100 mg/mL (Formulation 06-C)
C1105	Phase 1 study to evaluate the absolute bioavailability, PK, tolerability, and safety of a single dose or multiple doses of belimumab administered SC to healthy subjects	Single Dose – Groups 1-4: Belimumab 2 sequential SC injections of 120 mg each; 1 SC injection of 240 or 200 mg; or 1 IV infusion of 240 mg Multiple-Dose – Groups 5-6: Belimumab 2 sequential SC injections of 120 mg; or 1 SC injection of 200 mg on Days 0, 7, 14, and 21 Belimumab 200 mg/mL (Formulation 06-D)
BEL116119	Phase 1 study to investigate safety and PK following IV administration and SC administration of belimumab in healthy Japanese males	Belimumab 200 mg single dose; SC injection or IV infusion; Belimumab 200 mg/mL (Formulation 06-D)
BEL117100	Phase 1 study to evaluate the relative bioavailability, safety of belimumab administered SC to healthy subjects using PFS or AI	Belimumab 200 mg single dose; PFS SC or AI SC injection Belimumab 200 mg/mL (Formulation 06-D)
Phase 2 - Adults with SLE		
BEL112232	Phase 2 study to evaluate the safety, tolerability, and biological activity of 2 dosing schedules of belimumab administered SC to subjects with SLE	Belimumab 100 mg SC administration on Days 0, 7, 14 and then Q2wk or 200 mg SC administration on Days 0, 2, 4 and then 100 mg SC 3x/wk for 24 weeks followed by a 144-week continuation phase; SC injection Belimumab 100 mg/mL (Formulation 06-C)
200339	Phase 2 study to assess the suitability of an autoinjector (AI) for self-administration of belimumab by subjects with SLE in real-life conditions	Belimumab 200 mg weekly; AI SC injection; 8 weeks Belimumab 200 mg/mL (Formulation 06-D)
Controlled Repeat Dose Studies - Adults with SLE		
BEL112341	Phase 3 study to evaluate safety and efficacy of belimumab administered SC to subjects with SLE	Placebo or belimumab 200 mg weekly; SC injection; 52 weeks Belimumab 200 mg/mL (Formulation 06-D)

AI = autoinjector; IV = intravenous; PFS = prefilled syringe; Ph = phase; Q2wk = every 2 weeks; SC = subcutaneous; SLE = systemic lupus erythematosus.

2.4.2. Pharmacokinetics

The pharmacokinetic evaluation mainly aims at characterizing the pharmacokinetic profile after SC administration in order to support the proposed posology.

Pharmacokinetic data for SC administration of belimumab have been obtained from four Phase 1 studies in healthy volunteers and from two Phase 2 and one Phase 3 studies in SLE patients. In the belimumab SC development program, 2 liquid formulations and dosage strengths of belimumab in 3 different presentations have been used in clinical trials. Formulation 06-D is the final formulation intended for marketing.

Analytical methods

Concentrations of belimumab in human serum samples from all SC clinical studies were determined using validated bioanalytical immunoassay methods with an LLQ of 100 ng/mL of belimumab in human serum.

Pharmacokinetic data analysis

Standard non-compartmental methods were used to evaluate rich data in the individual single-dose studies. Evaluation of data from multiple-dose groups was performed by compartmental methods using Phoenix WinNonlin software. Sparse data from studies BEL112341, C1105 and BEL116119 were analysed using non-linear mixed effect modelling approach. A total of 688 subjects across 3 studies receiving belimumab administered SC and IV were included in the population PK analysis. The subject population comprised 584 females and 104 males with ages ranging from 18 to 77 years and weights ranging from 34 to 138 kg (median weight, 67.0 kg). There were white (61%), Asian (20%), Alaska Native or American Indian (6%) and African American (11%) subjects; 26% were of Hispanic/Latino ethnicity in the dataset.

Absorption

The absolute bioavailability of SC administered belimumab was evaluated in three studies in healthy volunteers.

In Study C1105 the absolute bioavailability of belimumab following a single SC administration (final formulation 06 D) in healthy US subjects ranged from a mean of 74% to 82%. The absolute bioavailability in the study BEL116119 in Japanese subjects (formulation 06-D, prefilled syringe) was 78%. In the study C1058 the absolute bioavailability of the early formulation 06-C was 67%.

Study BEL117100 was a randomized, parallel-group, open-label, single-dose study of belimumab in healthy subjects. The study was designed to evaluate the relative bioavailability of a single dose of belimumab (200 mg) when self-administered SC (formulation 06-D) by healthy subjects using an autoinjector compared to a pre-filled syringe. The two injection devices, prefilled syringe and autoinjector, were bioequivalent. For both AUC and Cmax the ratios of the GLS means were close to unity and the 90% CI of the ratios within the conventional bioequivalence limits of 80-125%.

Injections into the thigh resulted in slightly higher serum concentrations compared to injections into the abdomen regardless of device in BEL117100 (17% for prefilled syringe and 8% for autoinjector in terms of AUC and 11% and 13% for Cmax). The effect of different injection sites, thigh and abdomen, on belimumab PK was also evaluated in Study C1105. For both AUC and Cmax the 95% CI were overlapping indicating no significant difference between injection in thigh or abdomen.

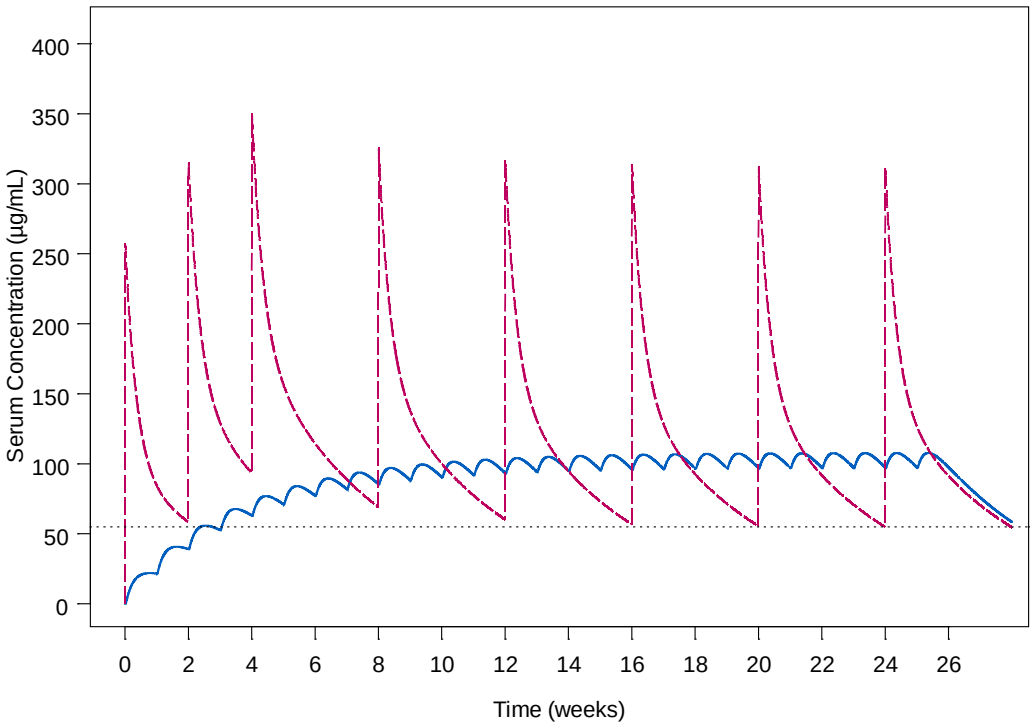
After switching from IV dosing of 10 mg/kg every 4 weeks to SC administration of the proposed dose of 200 mg once weekly a new steady state was in general reached after about 2-4 weeks (study 200339). In this study patients could switch after an interval of 1-4 weeks after the last IV dose. For subjects who switched to SC dosing <1.5 week after the last IV dose the serum concentrations were approx. 50% higher at week 1 of SC dosing compared to week 8, i.e. there was a transient increase in

serum concentration after initiation of SC dosing. For patients who used a drug free interval of 2-4 weeks the concentrations at week 1 and week 8 were comparable.

Simulations

Based on simulations with population PK data, steady state Cavg after SC administration of 200 mg once weekly was comparable to IV administration of 10 mg/kg every four weeks. Steady state concentrations were reached after approximately 11 weeks after SC dosing (Figure 5).

Figure 5. Comparison of Simulated IV and SC Exposure



The impact of shifting the day of dosing on the belimumab concentrations was evaluated using simulations using the SC population PK model. Administration of an additional dose one day after the scheduled dose followed by weekly administration relative to the new dosing day resulted in a transient increase in Cmax of approximately 20%.

The impact of missing a dose and then taking the missed dose one day before the next scheduled dose resulted in a transient decrease in Cmin by approximately 20%. After administration of the next scheduled dose (i.e. one day after the “make-up” dose), there was a small temporary increase in Cmax by 3%.

The impact of switching from IV to SC administration was also simulated. In accordance with the results from study 200339, there was a transient increase in serum concentration when a switching interval of 1 week was used. When a longer interval of 3-4 weeks was simulated, SC Cmin levels were above IV SC levels. However, steady state levels appears not be attained until approx. four weeks after the switch.

Distribution

Based on the population PK analysis the volume of distribution of belimumab at steady-state (Vss) is 4.95 L.

Elimination

The systemic clearance estimated from the belimumab SC population PK analysis was 204 mL/day. The terminal t1/2 estimated from the population PK analysis was 18.3 days which was similar to that estimated in the IV population PK analysis (19.4 days).

Dose proportionality and time dependencies

Dose proportionality data is very limited but there are no strong indications of deviations from dose proportionality. No further investigation is required since only one dose level of 200 mg is recommended.

There are no indications that the duration of dosing has no substantial effect on PK of belimumab SC.

Special populations

Intra- and inter-individual variability

Inter-individual variability was moderate; 25-44% for AUC and 25-33% for Cmax in healthy volunteers. Intra-individual variability was not evaluated.

Pharmacokinetics in target population

In the Phase 3 study BEL112341 steady state concentrations of belimumab were reached by approximately week 16 or earlier. The median concentrations at steady state after SC administration of 200 mg weekly (105 µg/mL) was close to steady state Cav after administration of 10 mg/kg every 4 weeks in the IV program (110 µg/mL).

No specific studies have been performed with respect to special populations. All available information is obtained from the population PK analysis.

In the population PK analysis there was a trend towards decreased clearance with decreased creatinine clearance, but the impact was not statistically significant. No dosage adjustments are considered necessary in patients with impaired renal function. Caution is however recommended in patients with severe renal impairment due to lack of data. Patients with hepatic impairment are considered unlikely to require dosage adjustments.

Gender or race did not have a statistically significant impact on belimumab SC PK in the population PK analysis.

The flat SC dosing leads to decreased exposure in patients with high weight and increased exposure in low weight patients. The decreased exposure in subjects with higher body weight or BMI did however not result in decreased efficacy.

There is very limited pharmacokinetic data in patients over 65 years of age.

There is no data in children or adolescents since Benlysta is not indicated in the paediatric population.

Belimumab SC exposure was not significantly affected by anti-drug antibodies (ADAs) in the population PK analysis. Given the small number of subjects with ADAs, an effect on ADAs on belimumab PK can however not be completely excluded.

Pharmacokinetic interaction studies

No in vivo interaction studies have been conducted.

An in vitro evaluation of the effect of BLyS on mRNA levels of CYP450 enzymes has been conducted. Although no effect was seen, no firm conclusion can be drawn since cytokine mediated drug-drug interactions cannot currently be predicted using in vitro data.

2.4.3. Pharmacodynamics

The population PK and PK/PD analysis was based on PK data from 3 studies: C1105, BEL112341 and BEL116119 and PD data from the pivotal study BEL112341.

Mechanism of action

Belimumab is a recombinant human IgG1λ monoclonal antibody that binds and antagonizes the biological activity of soluble B lymphocyte stimulator (BLyS, also known as BAFF) protein, a member of the tumor necrosis factor (TNF) ligand superfamily that promotes the survival of B lymphocytes.

Primary and Secondary pharmacology

High serum levels of soluble human B-lymphocyte stimulator (BLyS) have been shown to be associated with SLE disease activity [Petri, 2008b] and to increase the risk of clinically meaningful flare over the following year [Petri, 2013]. Given this association, targeting the BLyS pathway appears to be a mechanism for the treatment of SLE. Pharmacodynamic responses to belimumab are consistent with this mechanism of neutralizing BLyS.

In study BEL112341, belimumab SC significantly reduced circulating CD19+, CD20+, transitional and naïve B cells, the SLE B cell subset, and plasma cells at Week 52. Reductions in transitional and naïve B cells and the SLE B cell subset were observed as early as Week 8 and were sustained to Week 52.

A significant mean percent reduction from baseline in IgG was observed by Week 8 in the belimumab 200 mg SC group compared with placebo and was maintained throughout the treatment period, with an adjusted mean percent increase of 0.9% for placebo and 9.5% reduction for belimumab at Week 52. Reductions in IgA and IgM levels were also observed starting at Week 8 for IgA and Week 16 for IgM. These were maintained throughout the treatment period with a mean adjusted percent reduction of 11.7% in IgA and 32.4% in IgM at Week 52 in belimumab-treated subjects.

Immunoglobin and B cell response in study BEL112341 are compared to the pivotal IV study C1056 in the table below (study C1057 did not assess B cell subsets), illustrating that immunoglobin and B cell changes were consistent between the SC and IV studies.

Table 6: Median Percent Change from Baseline in Biomarkers at Week 52: C1056 vs. BEL112341

	C1056 (IV)			BEL112341 (SC)	
Parameter[a]	Placebo	1 mg/kg	10 mg/kg	Placebo	200 mg
Serum Immunoglobulins					
IgG	-0.8	-13.5	-14.4	0.7	-11.4[b]
IgM	-0.47	-28.2	-30.8	-4.2	-29.5[b]
IgA	-0.65	-16.1	-17.7	0.9	-12.9[b]
B cells					
CD19+	-10.4	-48.2	-48.5	-9.9	-57.9[b]
CD20+	-9.2	-46.1	-46.1	-10.6	-57.0[b]
Naïve (CD19+/CD20+/CD27-)[c]	-8.9	-66.7	-69.6	-10.6	-70.4[b]
Activated (CD19+/CD20+/CD69+)[c]	-15.8	-40.5	-45.1	-46.8	-54.5
Memory (CD19+/CD20+/CD27+)[c]	0	50.0	35.0	-20.2	22.2[b]
Plasmacytoid (CD19+/CD20+/CD138+)[c]	-14.4	-50.6	-65.8	-38.8	-50.9
SLE subset (CD19+/CD27BRIGHT/ CD38BRIGHT)	6.1	-23.7	-38.5	-18.2	-56.4[b]
Plasma (CD20-/CD138+)	-0.28	-21.6	-34.9	-47.5	-63.6[b]
Transitional CD19+/CD24b+/CD38BRIGHT+/CD27-	NA	NA	NA	-2.7	-62.3[b]

Source: CSR C1056 Final TE23.1_W76 -TE23.3_W76, TE29.1_W76 -TE29.9_W76; CSR BEL112341 Table 4.1 and Table 104.14

a. Baseline values by dose group are provided in the source tables
b. Denotes p-value <0.05. P-values are from a Wilcoxon rank sum test comparing belimumab SC and placebo (not reported in this table for belimumab IV).
c. Reported in C1056 without "CD19+/"

NA: not assessed.

No new studies on secondary pharmacology were conducted for the belimumab SC formulation development program.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics has been well characterised in both healthy volunteers and in SLE patients. Belimumab concentrations in serum were evaluated using validated bioanalytical methods.

Two devices are proposed for marketing; a prefilled syringe (PFS) and an autoinjector (AI). The PFS was used in the pivotal Phase 3 study. The AI was demonstrated to be bioequivalent to the PFS in a well-designed relative bioavailability study.

For patients switching from IV to SC dosing, an interval of 1-4 weeks is proposed in the SmPC. In study 200339 subjects who switched to SC dosing <1.5 week after the last IV dose the serum concentrations were approx. 50% higher at week 1 compared to week 8, i.e. there was a transient increase in serum concentration after initiation of SC dosing, indicating that a switching interval of <1.5 weeks may be somewhat short. Similar results were obtained in the simulations. It is however not anticipated that a 1-4 week switching interval would have a negative safety impact.

Based on the simulations of shifting in administration day the transient increase in Cmax is unlikely to be of clinical relevance. The increase in Cmax was modest (<20%) and maximum concentrations still lower than after IV administration. The simulation may be considered a worst-case scenario to evaluate the maximum increase in serum concentrations after a shift in dosing schedule. The simulations support the SmPC wording that a new dose can be given on the newly preferred day of the week and that the patient should continue with the new weekly schedule from that day.

Based on the simulated data, the impact of a missed dose appears to be minor. In case a dose is missed and not administered until one day prior to the next scheduled dose, Cmin levels were temporarily decreased, but were still higher than expected Cmin after IV dosing, and unlikely to have any clinical relevance. The simulations support the SmPC wording that, if a dose is missed, it should be administered as soon as possible but that it is not necessary to administer two doses on the same day.

The activity of drug metabolising enzymes ie CYPs can be modified during altered immunological states. Belimumab is an antibody directed against BLyS and can therefore be a cytokine modulator. This was addressed in a new in vitro study, evaluating the effect of BLyS on mRNA levels of CYP450 enzymes. Although no effect was seen, no firm conclusion can be drawn since cytokine mediated drug-drug interactions cannot currently be predicted using in vitro data. Information, describing the lack of information regarding cytokine mediated DDIs, has therefore been included in section 4.5 of the SmPC accordingly.

The data on patients >65 years are limited to <1.8% of the population studied in clinical trials. This is reflected in the SmPC together with a statement that treatment of elderly patients is not recommended unless the benefits are expected to outweigh the risks. The lack of data for some patient groups (e.g. elderly and patients with severe SLE affecting the kidneys or nervous system) is reflected in the RMP as missing information including appropriate pharmacovigilance measures.

2.4.5. Conclusions on clinical pharmacology

The CHMP considers that data submitted on pharmacology are sufficient for this application.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dose response studies with the to-be-marketed formulation (06-D) were conducted.

2.5.2. Main study(ies)

Study BEL112341:

A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) Administered Subcutaneously (SC) to Subjects with Systemic Lupus Erythematosus (SLE) - Open-label phase - End of Study report

A single pivotal study (BEL 112341) was conducted to support the SC formulation. This was a Phase 3, multicenter, international, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab administered SC in adult subjects with active SLE. In addition to receiving stable standard therapy, eligible subjects were randomized to 1 of 2 treatment groups in a 2:1 ratio: 200 mg belimumab weekly or placebo SC weekly.

For the most part, the critical design elements of this SC study were the same as those utilized for the previous pivotal Phase 3 IV program. In BEL112341, subjects were randomized to belimumab or placebo (2:1 ratio) and study agent was administered SC on Day 0 and weekly thereafter to Week 51.

In C1056 and C1057, belimumab was administered IV on Days 0, 14 and 28 and every 28 days thereafter to Week 72 or Week 48, respectively. The primary endpoint for all 3 studies was at Week 52 (C1056 had an additional double-blind period out to Week 76).

Methods

Study Participants

The inclusion criteria for the SC study were generally the same as the Phase 3 IV studies as following:

- At least 18 years of age;
- Clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria;
- Clinically active SLE disease, defined as a SELENA SLEDAI disease activity score of ≥8 at screening. Subjects had to have unequivocally positive autoantibody test results, either from 2 independent time points within the study screening period or 1 positive historical test result and 1 positive test result during screening. Autoantibody test results obtained in the screening period were considered positive if the anti-nuclear antibody (ANA) titer was ≥1:80 and/or anti-double stranded deoxyribonucleic acid (antidsDNA) serum antibody was ≥30 IU/mL.
- Be on a stable SLE treatment regimen ≥30 days prior to Day 0 wherein stable treatment consisted of any of the following (alone or in combination): prednisone or equivalent (from 0 to 40 mg/day when used in combination with other SLE treatment or from 7.5 to 40 mg/day when used alone), antimalarials (e.g. hydroxychloroquine, chloroquine, quinacrine), non-steroidal anti-inflammatory drugs (NSAIDs), or any immunosuppressive or immunomodulatory therapy (i.e., methotrexate, azathioprine, leflunomide, mycophenolate, calcineurin inhibitors [e.g. tacrolimus, cyclosporine], sirolimus, oral cyclophosphamide, 6-mercaptopurine, mizoribine or thalidomide).

The key exclusion criteria included the following:

- Severe lupus kidney disease (defined as proteinuria > 6 g/24 hour or equivalent using spot urine protein to creatinine ratio, or serum creatinine > 2.5 mg/dL),or severe active lupus nephritis requiring acute therapy not permitted by protocol;
- Central nervous system lupus;
- Pregnancy;
- Have received treatment with any B cell targeted therapy. (However, for centers in US, UK, Spain, Portugal, Sweden and Denmark, following local amendment to the protocol, treatment with B cell targeted therapy ≥1 year prior to screening was allowed; otherwise, receipt of any B cell target therapy at any time prior to screening was not allowed);
- Receipt within 1 year prior to Day 0 of investigational biologics other than B cell targeted therapy, or of abatacept;
- Receipt within 90 days prior to Day 0 of any anti-tumor necrosis factor (TNF) therapy, intravenous (IV) cyclophosphamide, interleukin-1 receptor antagonist (anakinra), IV immunoglobulin (IVIG), prednisone >100 mg/day, or plasmapheresis;

- Receipt within 60 days prior to Day 0 of investigational nonbiologics, any new immunosuppressive/immunomodulatory agent, anti-malarial, or NSAID, or any steroid injection;
- Receipt within 30 days prior to Day 0 a live vaccine or a change in dose of a corticosteroid, other immunosuppressive/immunomodulatory agent, anti-malarial, or NSAID;
- Subjects with evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) in the last 2 months or who, in the investigator's opinion, posed a significant suicide risk;
- Having required management of acute or chronic infections (ie, chronic ongoing treatment with suppressive therapy or hospitalization or use of parenteral antibiotics within 60 days of Day 0);
- History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies;
- ≥Grade 3 laboratory abnormality (some exceptions permitted).

Treatments

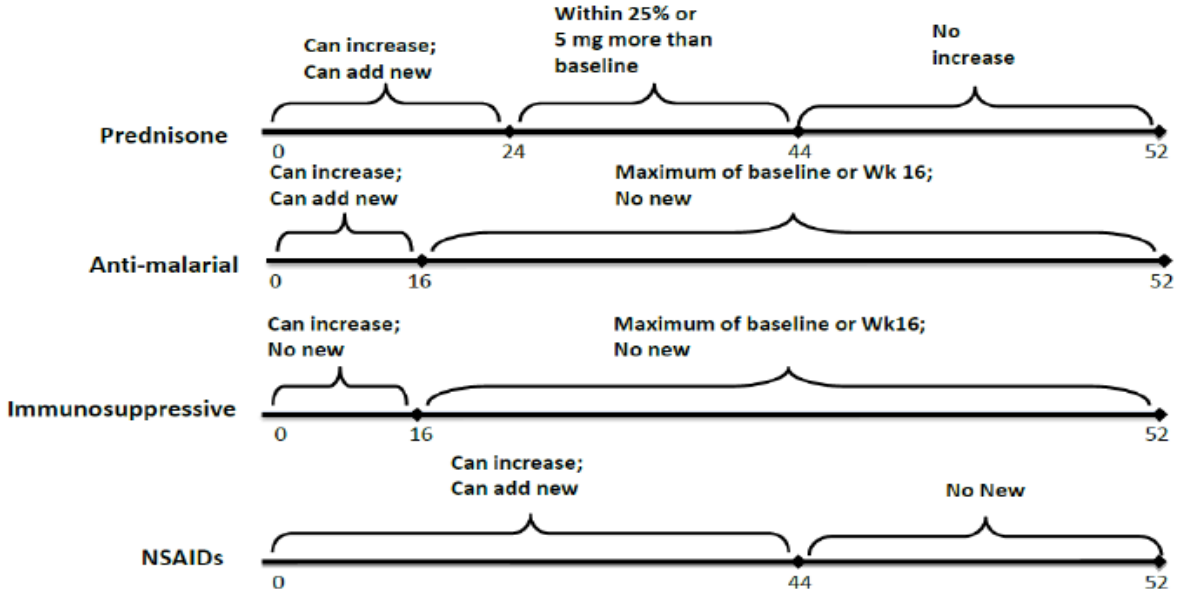
200 mg belimumab or placebo control was administered weekly by SC injection. No premedication was stipulated by the study protocol.

After randomization, subjects were dosed with blinded study agent on Day 0 and then weekly through 51 weeks of treatment. Subjects who completed the initial treatment period (51 weeks of treatment with a final assessment at Week 52) were given the option to receive open label belimumab 200 mg SC weekly during an additional extension phase for 6 months.

The 1st and 2nd doses of belimumab were administered under supervision at the study site on Day 0 and Day 7 (± 1 day). Subjects were to remain at the clinic for 3 hours following the first two doses of the study agent for observation. At the discretion of the investigator, subjects/caregivers who were adequately trained were allowed to administer all subsequent doses at home.

Comprehensive concomitant medication controls were implemented (Figure 6).

Figure 6: Overview of concomitant medication rules in BEL112341



Prohibited medication at any time during the study included other investigational agents (biologic or non-biologic), anti-TNF therapy, other biologics, intravenous immunoglobulin, IV cyclophosphamide, and plasmaferesis.

Objectives

Study objectives were to evaluate the efficacy of belimumab administered SC in adult subjects with SLE and the safety and tolerability of belimumab administered SC in adult subjects with SLE.

Outcomes/endpoints

The primary efficacy endpoint was the SLE responder 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 Physician's Global Assessment (PGA), AND no new British Isles Lupus Assessment Group (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 endpoints were:

- Time to first severe flare (as measured by the modified SLE Flare Index [SFI]); and
- Percent of subjects whose average prednisone dose has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 in subjects receiving greater than 7.5 mg/day at baseline.

Serum belimumab concentrations were the pharmacokinetic endpoint.

The safety endpoints were: adverse events (AEs), serious AEs (SAEs), adverse events of special interest, clinical laboratory parameters, immunogenicity, and vital signs.

Sample size

Approximately 816 subjects were planned to be randomized and treated in the study, with a target of at least 544 subjects receiving belimumab and 272 subjects receiving placebo. This sample size provided at least 90% power at a 5% level of significance to detect a minimum of 12% absolute improvement in response rate for the 200 mg belimumab group (assumed rate = 56%) relative to the placebo group (assumed rate = 44%) at Week 52. The selection of the 12% absolute improvement was based on the observed response rate in the Phase 3 IV studies.

Randomisation

Subjects were assigned to 1 of 2 treatment groups, 200 mg belimumab or placebo control, in a 2:1 ratio in accordance with the randomization schedule via an electronic data capture (EDC)-based IWRS. The randomization was stratified by screening SELENA SLEDAI score (8-9 vs. ≥10), complement level (C3 and/or C4 low vs. other) and race (Black vs. Other).

Blinding (masking)

The study was blinded to belimumab. Belimumab for injection was supplied as double blinded prefilled syringes. The study agent was distributed by the site pharmacist or designee. Except for a limited number of safety oversight personnel, all study site personnel, the subject, the sponsor and the CRO were to remain blinded to the study agent received and to the results of certain biomarker 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. The Sponsor's Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind treatment codes in the event of a SAE. Other GSK staff remained blinded to subjects' treatment until data through the Week 52 primary efficacy analysis were locked and unblinded.

Statistical methods

For the analysis of the primary and the major secondary efficacy endpoints, a step-down sequential testing procedure was used to control the overall type 1 error rate. With this procedure, the primary and two major secondary endpoints were evaluated for statistical significance based on a pre-specified sequence for interpretation: (1) SRI response rate at Week 52, (2) time to first severe SLE flare, and (3) percent of subjects with average prednisone dose that has been reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52. Specifically, endpoints were tested in the sequence above (2-sided alpha=0.05) provided that statistical significance was achieved by all prior tests.

A logistic regression model was used to estimate the odds of an SRI response. The independent variables in the model were treatment group, baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

Overall the statistical methods are adequate for the analysis of the study data. For the analyses, baseline (rather than screening) values of the respective stratification factors were used since baseline values represent the status of the subject at the time study treatment is first administered. However, there was a high level of consistency between screening and baseline values of SELENA SLEDAI and complement.

Results

Recruitment and Participant flow

A total of 1427 subjects were screened to yield 839 randomized subjects, of whom 836 received at least 1 dose of study agent. The most common reasons for failed screening were failing to meet inclusion (n=347) or exclusion (n=180) eligibility criteria. The 836 subjects (280 in the placebo group and 556 in the belimumab 200 mg SC group) in the ITT population were enrolled across 177 sites in 30 countries. Half the subjects in the ITT population were from the USA (28.3%) and Eastern Europe (22.5%); other regions where the study was conducted were the Americas excluding the USA and Canada (20.6%), Asia (20.6), and Western Europe (8.0). Most subjects (81.0%) completed the study through Week 52 (see Table 7).

Table 7: Completion status through Week 52 in BEL112341 (ITT population)

	Number (%) of Subjects		
	Placebo N=280	Belimumab 200 mg N=556	Total N=836
Completed Week 52 visit	214 (76.4)	463 (83.3)	677 (81.0)
Withdrawn prior to Week 52	66 (23.6)	93 (16.7)	159 (19.0)
Adverse Event	25 (8.9)	40 (7.2)	65 (7.8)
Subject Request	15 (5.4)	12 (2.2)	27 (3.2)
Disease Progression/Lack of Efficacy	10 (3.6)	15 (2.7)	25 (3.0)
Other	4 (1.4)[a]	14 (2.5)[a]	18 (2.2)
Lost to Follow-up	2 (0.7)	6 (1.1)	8 (1.0)
Protocol Violation	3 (1.1)	4 (0.7)	7 (0.8)
Investigator Decision	5 (1.8)	1 (0.2)	6 (0.7)
Lack of Compliance	2 (0.7)	1 (0.2)	3 (0.4)

Source: Table 1.4

a. 1 subject in the placebo group (0.4%) and 6 subjects in the belimumab 200 mg SC group (1.1%) withdrew due to pregnancy (Source: Listing 1.3).

Conduct of the study

The original protocol (dated on 03 August 2011) was amended 8 times during the study. Five amendments applied to all sites and 3 amendments were country-specific.

Baseline data

The summary of demographics and baseline disease characteristics is provided on the section "*Analysis performed across trials (pooled analyses and meta-analysis".*

Numbers analysed

The numbers of subjects analysed in BEL112341 study is showed in the table 8.

Table 8: Numbers of subjects in the analysis populations in BEL112341

	Placebo	Belimumab 200 mg	Total
Randomized	280	559	839
Population			
Intent-to-Treat[a]	280	556	836
Per Protocol[b]	268	521	789
Completers[c]	214	463	677
As-treated[d]	280	556	836
PK[e]	1[f]	554	555

Source: Table 1.2

a. All subjects who were randomized and treated with at least one dose of study treatment. If a subject received an incorrect treatment, the subject was assigned to a treatment group according to the treatment that the subject was randomized to receive, regardless of the actual treatment received.
b. All subjects who were randomized and treated with at least one dose of study treatment excluding subjects with major protocol deviations.
c. All subjects who completed all 52 weeks of the planned double-blind treatment period.
d. All subjects who received at least one dose of study treatment. Subjects are assigned to treatment groups according to the actual treatment administered to the subject. If a subject received an incorrect treatment, the subject was assigned to a treatment group according to the treatment received for >50% of the time.
e. All subjects included in the As-Treated population for whom at least one post belimumab treatment PK sample was obtained and analyzed.
f. One subject was randomized to placebo and discontinued the study due to protocol violation . Six days before the 8-week follow-up visit, the subject received IV belimumab. Because the subject's blood sample had a serum belimumab concentration at a post-baseline visit, she was assigned to the PK population (Source: Listing 1.2, Listing 1.3, Listing 1.10, Listing 5.1).

Outcomes and estimation

Primary endpoint analyses results

The SRI response at Week 52 was positive and statistically significant (48.4% placebo, 61.4% belimumab, p=0.0006) (table 9). Also, each of the 3 components reached statistical significance (p<0.05)

(Table 10).

The statistically significant differences in the SRI response were observed by Week 16 and sustained through Week 52 (Figure 7).

Table 9: SRI Response at Week 52 (dropout/treatment failure=NR) in BEL112341

	Placebo N=280	Belimumab 200 mg N=556
Response (primary efficacy analysis)[a], n/n (%)	135/279 (48.4)	340/554 (61.4)
Observed difference vs. placebo (%)	-	12.98
Odds ratio (95% CI)[b] vs. placebo	-	1.68 (1.25, 2.25)
p-value[b]	-	0.0006

Source: CSR BEL112341 Table 2.1

a. Three ITT subjects did not have a baseline PGA assessment and, therefore, do not contribute to SRI/component analyses.
b. Odds Ratio (95% confidence interval) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

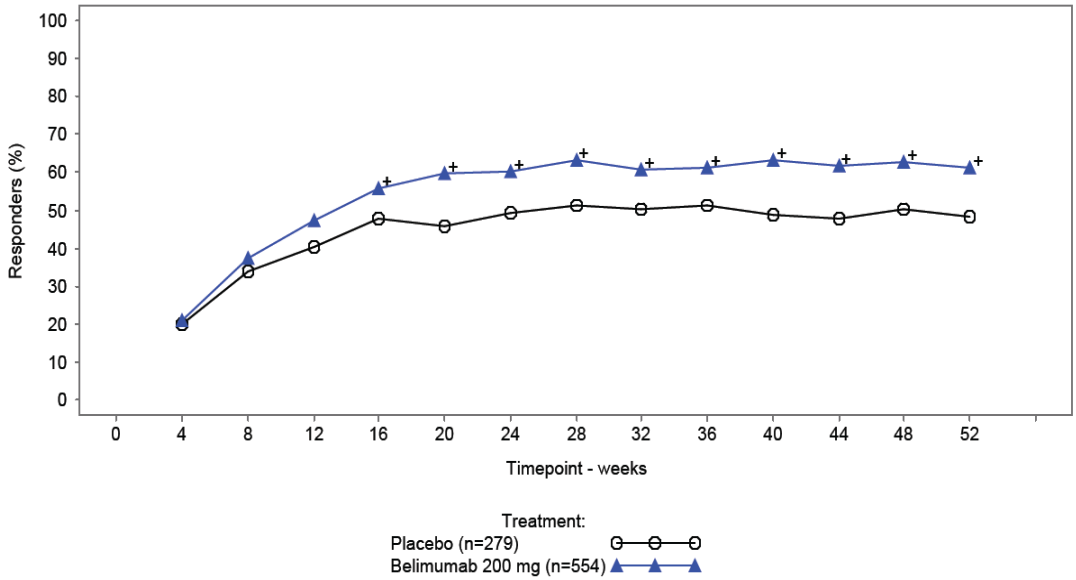
Table 10: The 3 components of SRI response at Week 52 in BEL112341

	Placebo N=280	Belimumab 200 mg N=556
4-point reduction in SELENA SLEDAI[a], n/n (%)	137/279 (49.1)	345/554 (62.3)
Odds ratio (95% CI)[b] vs. placebo	-	1.69 (1.26, 2.27)
p-value[b]	-	0.0005
No worsening in PGA[a], n/n (%)	203/279 (72.8)	450/554 (81.2)
Odds ratio (95% CI)[c] vs. placebo	-	1.61 (1.15, 2.27)
p-value[c]	-	0.0061
No new 1A/2B BILAG domain scores[a], n/n (%)	207/279 (74.2)	448/554 (80.9)
Odds ratio (95% CI)[d] vs. placebo	-	1.46 (1.04, 2.07)
p-value[d]	-	0.0305

Source: CSR BEL112341 Table 2.3

a. Three ITT subjects did not have a baseline PGA assessment and therefore, do not contribute to SRI/component analyses.
b. Odds Ratio (95% CI) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).
c. Baseline PGA was also included in the model.
d. Baseline BILAG domain involvement (at least 1A/2B vs. at most 1B) was also included in the model.

Figure 7: SRI Response by Visit through Week 52 in BEL112341



Source: CSR BEL112341 Figure 2.8. Note: + denotes p-value <0.05

Note: p-value is from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

Sensitivity analyses of the primary endpoint

The prespecified sensitivity analyses were conducted for unadjusted response, LOCF response, completer response, and per protocol response.

The primary efficacy analysis at Week 52 was also repeated using the SLEDAI 2K proteinuria scoring rule which scores proteinuria as 4 points anytime the value is >0.5 g/24 h (rather than only with new onset or recent increase). The result of the SRI SLEDAI 2K analysis favored belimumab (odds ratio 1.83; 95% CI: 1.36, 2.46; p<0.0001) and was consistent with the primary efficacy analysis.

Analysis of the SRI was also performed using the EMA modified SRI response rate at Week 52. In the EMA modified endpoint, the 'No New BILAG 1A/2B domain score' component is replaced with 'No BILAG 1A/2B domain score' in the SRI.

Major secondary endpoints

Time to first severe SFI flare over 52 weeks

Subjects in the belimumab 200 mg SC group had a 49% lower risk of experiencing a severe SFI flare compared with placebo; 10.6% of subjects in the belimumab group had a severe flare vs. 18.2% in the placebo group (hazard ratio [HR] 0.51; 95% CI: 0.35, 0.74; p=0.0004). Of those subjects experiencing a severe flare, the median number of days to first severe flare was 171.0 (25th, 75th percentile: 57.0, 257.0) in the belimumab group and 118.0 (25th, 75th percentile: 62.0, 259.0) in the placebo group.

Percent of subjects whose average prednisone dose was reduced by ≥ 25% from baseline to ≤7.5 mg/day during Week 40 through Week 52

A greater proportion of subjects on belimumab 200 mg SC (18.2%) than placebo (11.9%) reduced their prednisone dose; the difference approached statistical significance (p=0.0732) (Table 11).

Table 11: Prednisone Reduction by ≥25% from Baseline to ≤7.5 mg/day during Week 40 through Week 52 (DO/TF=NR) in BEL112341

	Placebo N=280	Belimumab 200 mg N=556
Reduction in prednisone[a], n/n (%)	20/168 (11.9)	61/335 (18.2)
Observed difference vs. placebo (%)	-	6.30
Odds ratio (95% CI)[b] vs. placebo	-	1.65 (0.95, 2.84)
p-value[b]	-	0.0732

Source: CSR BEL112341 Table 2.63

Note: All corticosteroids are converted to a prednisone equivalent average daily dose (mg/day).

a. Includes only subjects with baseline prednisone >7.5 mg/day.

Odds Ratio (95% CI) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline prednisone dose, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

This analysis was only conducted in subjects with baseline prednisone use >7.5 mg per day. This was the case for only a subgroup of subjects (503/836, 60.2%), and, similar to the IV studies, there was no requirement for forced tapering of steroids in the study.

Other secondary endpoints

Disease activity

Results for the durable SRI response from Week 44 through Week 52 analysis were similar to the primary analysis. A greater proportion of subjects in the belimumab 200 mg SC group (54.3%) had a durable SRI response defined as a sustained SRI response from Week 44 through Week 52 compared with placebo (40.9%) (odds ratio 1.71; 95% CI: 1.27, 2.30; p=0.0004).

The median number of days to first SRI response that was maintained through Week 52 was 235 days (=33.6 weeks) in the belimumab 200 mg SC group vs. 338 days (=48.3 weeks) in the placebo group. For this SRI endpoint, a greater proportion of subjects in the belimumab group (61.4%) were responders compared with the placebo group (48.4%) (Hazard Ratio 1.48; 95% CI: 1.21, 1.81; p=0.0001).

No differences were observed for the mean change from baseline to Week 52 in the SLICC/ACR damage index (SDI) with adjusted mean changes of 0.1 for the placebo group and 0.0 for the belimumab group (p=0.1174).

Flares

Subjects in the belimumab 200 mg SC group had a 22% lower risk of a first SFI flare (any severity) over 52 weeks (Hazard ratio 0.78; 95% CI: 0.65, 0.93; p=0.0061).

The adjusted rate ratio for SFI flares per subject-year from Day 0 to Week 52 was 19% lower for the belimumab 200 mg SC group compared to placebo group (p=0.0186). For severe SFI flares, the adjusted rate ratio per subject-year from Day 0 to Week 52 was 46% lower for the belimumab group compared to the placebo group (p=0.0128).

Renal flares

Overall, by Week 52, 21 (7.5%) of subjects in the placebo group experienced a renal flare in comparison to 26 (4.7%) in the belimumab group (Hazard Ratio 0.57; 95% CI: 0.32, 1.01; p=0.0532). Among subjects with baseline proteinuria >0.5 g/24 h, 13 (27.1%) in the placebo group experienced a renal flare, in comparison to 11 (11.1%) in the belimumab group (Hazard Ratio 0.40; 95% CI: 0.18, 0.90; p=0.0272).

The percent of subjects with at least one renal flare over the 52-week study period was small, likely a reflection of the eligibility criteria and the low rates of renal disease involvement at baseline.

Cumulative prednisone dose

The mean ± SD cumulative prednisone dose was 4567.3 ± 5981.53 mg over 52 weeks in the placebo group and 3933.8 ± 3660.76 mg over 52 weeks in the belimumab group.

Health outcome results

Subjects in the placebo and belimumab groups had an increased (improved) mean FACIT-Fatigue Scale score; the improvement was greater for subjects in the belimumab group. At Week 52, the adjusted mean change was 2.7 for the placebo group in comparison to 4.4 in the belimumab group (treatment difference 1.6; 95% CI 0.3, 2.9; p=0.0130; Among subjects in the placebo group, 101 (36.1%) experienced improvement in FACIT fatigue score exceeding the MCID (≥4) at Week 52, in comparison to 246 (44.4%) of subjects in the belimumab group (odds ratio 1.42, 95% CI 1.05, 1.94, p=0.0245).

Ancillary analyses

Subgroup analyses for the primary efficacy endpoint were conducted by age (<65 vs. ≥65 years), gender, baseline body weight quartiles and BMI categories, race, region, disease activity, baseline prednisone use, baseline average daily prednisone dose (yes vs. no), baseline MMF use, baseline medications, and immunogenicity status (Table 12).

Table 12: Primary Response at Week 52 by subgroups in BEL112341 (ITT Population)

	Placebo N=280	Belimumab 200 mg N=556
Overall	135/279[a] (48.4)	340/554[a] (61.4)
Age Group		
<65 years	134/272 (49.3)	333/542 (61.4)
≥65 years	1/7 (14.3)	7/12 (58.3)
Gender		
Male	6/12 (50.0)	18/35 (51.4)
Female	129/267 (48.3)	322/519 (62.0)
Baseline Body Weight Quartiles		
Q1 <55.05	38/70 (54.3)	89/139 (64.0)
Q2 55.05 - <65.15 kg	32/66 (48.5)	79/141 (56.0)
Q3 65.15 - <78.25 kg	36/73 (49.3)	88/135 (65.2)
Q4 ≥78.25 kg	29/70 (41.4)	84/139 (60.4)
Baseline BMI Categories		
Underweight	11/16 (68.8)	25/35 (71.4)
Normal	62/124 (50.0)	152/267 (56.9)
Overweight	34/75 (45.3)	84/123 (68.3)
Obese	28/64 (43.8)	79/128 (61.7)
Race (Black/Other)		
Black	13/33 (39.4)	26/58 (44.8)
Other	122/246 (49.6)	314/496 (63.3)
Race		
White/Caucasian	81/165 (49.1)	210/336 (62.5)
African American	12/30 (40.0)	24/55 (43.6)
Asian	32/63 (50.8)	70/120 (58.3)
Native American	10/21 (47.6)	36/43 (83.7)
Race Stratification		
Black	11/29 (37.9)	23/54 (42.6)
Other	124/250 (49.6)	317/500 (63.4)
Country Region		
USA/Canada[b]	28/84 (33.3)	73/152 (48.0)
Americas excluding USA and Canada	35/57 (61.4)	93/115 (80.9)
Western Europe/Australia/Israel[c]	8/18 (44.4)	25/48 (52.1)
Eastern Europe	33/59 (55.9)	83/129 (64.3)
Asia	31/61 (50.8)	66/110 (60.0)
Baseline SELENA SLEDAI Score		
≤9	46/111 (41.4)	98/202 (48.5)
≥10	89/168 (53.0)	242/352 (68.8)
Baseline C3 or C4 Levels		
No low C3 or C4	74/153 (48.4)	167/285 (58.6)
Low C3 and/or C4	61/126 (48.4)	173/269 (64.3)
Baseline C3/C4 Levels and Anti-dsDNA		
Not at least one C3/C4 low and anti-dsDNA ≥30 IU/mL	84/171 (49.1)	181/308 (58.8)

	Placebo N=280	Belimumab 200 mg N=556
At least one C3/C4 low and anti-dsDNA ≥30 IU/mL	51/108 (47.2)	159/246 (64.6)
Baseline Anti-dsDNA		
<30 IU/mL	40/86 (46.5)	90/152 (59.2)
≥30 IU/mL	95/193 (49.2)	250/402 (62.2)
Baseline Average Daily Prednisone Dose		
0 mg/day	18/39 (46.2)	36/74 (48.6)
>0 - ≤7.5 mg/day	35/72 (48.6)	98/146 (67.1)
>7.5 mg/day	82/168 (48.8)	206/334 (61.7)
Baseline Prednisone Use		
Non-use	18/39 (46.2)	36/74 (48.6)
Use	117/240 (48.8)	304/480 (63.3)
Baseline Medications		
Other	108/212 (50.9)	261/421 (62.0)
Steroid, Antimalarial, and Immunosuppressant	27/67 (40.3)	79/133 (59.4)
Baseline MMF		
No MMF	120/245 (49.0)	306/484 (63.2)
MMF	15/34 (44.1)	34/70 (48.6)
Immunogenicity Status[d]		
Negative	135/279 (48.4)	340/553 (61.5)
Baseline Immunosuppressant Use		
Non-use	70/143 (49.0)	201/310 (64.8)
Use	65/136 (47.8)	139/244 (57.0)
Baseline SELENA SLEDAI Score		
≥8	128/256 (50.0)	327/517 (63.2)

Source: Table 2.1, Table 2.77, Table 2.78, Table 2.79, Table 2.80, Table 2.81, Table 2.82, Table 2.83, Table 2.84, Table 2.85, Table 2.86, Table 2.87, Table 2.88, Table 2.89, Table 2.90, Table 2.91, Table 2.92, Table 102.93, Table 102.99, Table 102.100

Note: SRI response is shown as n/n (%).

a. Three ITT subjects did not have a baseline PGA assessment and therefore, do not contribute to SRI/component analyses.
b. Although this category is labeled USA/Canada for purposes of consistency with previous belimumab studies, no subjects were enrolled by Canada.
c. Although this category is labeled Western Europe/Australia/Israel for purposes of consistency with previous belimumab studies, no subjects were enrolled by Australia or Israel.
d. For Immunogenicity Status, positive is not shown as no subjects were positive.

Age and gender

As most subjects were <65 years and female, the response in these subgroups was similar to the overall population. The relatively small number of subjects in the ≥65 years (n=19) and male (n=47) subgroups limits interpretation.

Body weight and BMI subgroups

The belimumab SC 200 mg fixed dosing represents a lower dosing regimen for those with higher body weight as compared with IV dosing at 10 mg/kg. However, a decrease in efficacy of belimumab SC 200 mg in relation to higher body weight was not observed. Rather, the higher weight quartiles, Q3 and Q4, as well as BMI categories overweight/obese showed the greatest treatment differences numerically. As this was not expected, the Applicant was requested to discuss whether this could be explained e.g. by differences in disease activity between the weight subgroups. However, baseline disease characteristics (e.g. in terms of mean and median SELENA SLEDAI score) and SLE medication profiles by body weight quartiles and BMI categories generally showed no clear imbalance. The numerically somewhat lower placebo response rate in the Q4 quartile and the overweight and obese

BMI categories may have contributed to the relatively larger treatment difference observed for these groups.

Region

For the USA/Canada subgroup 33.3% and 48.0% of the placebo and belimumab groups, respectively, met the SRI endpoint (odds ratio 1.85, 95% CI: 1.06, 3.22; p=0.0298) (BEL112341 CSR, Table 2.81). For the Americas excluding USA/Canada, 61.4% and 80.9% of the placebo and belimumab groups respectively met the SRI endpoint (odds ratio 2.66, 95% CI: 1.31, 5.39; p=0.0068). However, in Western and Eastern Europe, as well as Asia, the observed difference in SRI response vs. placebo was numerically lower (ranging from 7.6 to 9.2%) and not statistically significant.

As noted in the central advice (EMEA/H/SA/717/3/2011/III), efforts should be made to warrant that participants in the trial are sufficiently representative of the EU population. It appears that the region 'Americas excluding USA and Canada' is a major driver of the overall results. Various regional differences in response rates were observed in the previous pivotal IV studies. For example, subjects in the US/Canada in the pivotal IV studies had lower response rates in all 3 treatment groups compared with all other regions and there was a smaller treatment difference between belimumab and placebo treatment groups. At that time, these regional differences were not fully clarified but considered to be related to factors such as imbalances in baseline disease activity. No such imbalances were observed in the current BEL112341 study and, in spite of some numeric differences between the various regions, there were positive treatment differences vs. placebo for all regions. Several of the subgroups, including Western Europe, were limited in size which could explain some of the variability observed.

Disease activity

Primary response was evaluated for disease activity subgroups based on baseline values of SELENA SLEDAI score, C3 and/or C4, anti-dsDNA, steroid use and dose, MMF use and other baseline medications (use of steroid and antimalarial and immunosuppressant vs. not use of all these medications) for Study BEL112341. In addition, a subgroup of baseline C3/C4 levels and anti-dsDNA (at least one C3/C4 low and anti-dsDNA ≥30 IU/mL vs. not having these baseline levels) was evaluated for the primary endpoint and additional efficacy endpoints.

<u>Selena SLEDAI subgroup</u>

SRI response rates were lower for the SELENA SLEDAI subgroup ≤9 points (41.4% and 48.5% for placebo and belimumab respectively) and were higher for the SELENA SLEDAI subgroup ≥10 points (53.0% and 68.8% for placebo and belimumab 200 mg respectively) as compared to the overall treatment response rates (48.4% and 61.4% for placebo and belimumab, respectively) (CSR BEL112341, Table 2.88 and Table 2.1).

The SRI response rate at Week 52 for the SELENA SLEDAI subgroup ≥10 points (n=242) was statistically significantly different from placebo (15.77% difference, OR: 1.95 [1.34, 2.85], p=0.0005). This was not the case for the SELENA SLEDAI ≤9 subgroup (n=202) (7.1% difference, OR:1.33 [0.83, 2.13], p=0.2302).

<u>Anti-dsDNA subgroup</u>

The SRI response rate at Week 52 for the high anti-dsDNA (≥30 IU/mL) subgroup (n=402) was statistically significantly different from placebo (12.97% difference, OR: 1.70 [1.20, 2.40], p=0.0028). This was not the case for the <30 IU/mL subgroup (n=152) (12.70% difference, OR:1.67 [0.98, 2.84], p=0.0596) (CSR BEL112341, Table 2.89).

<u>Low complement subgroup</u>

The low C3 and /or C4 subgroup demonstrated a higher response rate (64.3%) than either the No low C3 and/or C4 subgroup or the overall treatment groups (58.6% and 61.4%, respectively) for the belimumab groups (CSR BEL112341, Table 2.90 and Table 2.1).

The SRI response rate at Week 52 for the low C3 and/or low C4 subgroup (n=269) was statistically significantly different from placebo (15.90% difference, OR: 1.92 [1.25, 2.95], p=0.0029). This was lower, although also significant, for the no low C3 or C4 subgroup (n=285) (10.23% difference, OR: 1.51 [1.02, 2.24], p=0.0406).

Low complement and positive anti-dsDNA subgroup

For subjects with low complement and high anti-dsDNA, belimumab treatment demonstrated a greater response rate relative to placebo (observed difference vs. placebo 17.41%; odds ratio 2.23; 95% CI: 1.36, 3.64, p=0.0014) as compared to the NOT low complement and high anti-dsDNA subgroup (observed difference vs. placebo 9.64%; odds ratio 1.46; 95% CI: 1.00, 2.14, p=0.0488).

Analyses of *time to first severe SFI flare* were also conducted for this subgroup. For subjects with low complement and high anti-dsDNA, the risk of flare was significantly reduced as 31.55 of subjects in the placebo group developed a severe flare vs. 14.1% in the belimumab group (hazard ratio 0.38 [0.24, 0.61), p<0.0001). The results for the NOT low complement and high anti-dsDNA subgroup were not significant, 9.9% subjects in the placebo and 7.8% of subjects in the belimumab group developed a severe flare (hazard ratio 0.76 [0.041, 1.41], p=0.3836).

The results were similar for the additional efficacy endpoint of time to first flare over 52 weeks (regardless of severity), i.e. statistically significant for the high but not the low disease activity subgroup (p=0.0145 and p=0.0942), respectively (CSR BEL112341, Table 2.26).

Findings for the other major secondary endpoint (percent of subjects whose average prednisone dose was reduced by ≥25% from baseline to ≤7.5 mg/day during Week 40 through Week 52) showed numerically greater response rates in the high disease activity (9.30% difference vs. placebo, OR: 2.08 [0.91, 4.77], p=0.0844) compared to the low disease activity subgroup (3.54% difference vs. placebo, OR: 1.31 [0.62, 2.74], p=0.4767) (CSR BEL112341, Table 2.64).

Summary of main study

The following tables summarise the efficacy results from the main study 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 13. Summary of Efficacy for trial BEL112341

Title: A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) Administered Subcutaneously (SC) to Subjects with Systemic Lupus Erythematosus (SLE) – Double-Blind Endpoint Analysis		
	BEL112341	
Study identifier	Randomised 2:1, double blind, parallel group, placebo controlled	
Design	Duration of screening phase:	35 days

	Duration of main phase: Duration of Extension phase:		52 weeks 6 months		
	Confirmatory: The SRI response rate in the 200 mg belimumab SC group (assumed rate=56%) is at least 12% higher than in the placebo group (assumed rate=44%)				
Hypothesis Treatments groups	Belimumab 200 mg/mL		200 mg (one injection) administered SC once weekly, number randomized n=559		
	Placebo (matching)		one injection administered SC once weekly, number randomized n=280		
Endpoints and definitions	Primary endpoint	SRI response rate at Week 52	SRI response defined as 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 time of assessment (at Week 52)		
	Key Secondary endpoint	Time to first severe flare	As measured by the modified SLE Flare Index [SFI]).		
	Key Secondary endpoint	Percent subjects with average prednisone dose reduced by ≥25% from baseline to ≤7.5 mg/day during Weeks 40-52 in those receiving >7.5 mg/day at baseline			
Study period	16 Nov 2011 – Ongoing; last subject last visit:13 Feb 2015 for the double-blind endpoint analyses				
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 subjects		556	280	p-value
	Primary endpoint SRI response rate n/n (%)		340/554 (61.4)	135/279 (48.4)	
	Observed difference vs. placebo Odd ratio (95% CI) vs. placebo		12.98 1.68 (1.25, 2.25)		0.0006
	Key secondary Time to first severe SFI flare n (%) Median time to first flare (days) Hazard ratio (95% CI) vs. placebo		59 (10.6) - (-,-) (0.35, 0.74)	51 (18.2) - (-,-)	0.0004
	Key secondary Percent subjects with average prednisone dose reduced n/n%		61/335 (18.2)	20/168 (11.9)	
	Observed difference vs. placebo Odd ratio (95% CI) vs. placebo		6.30 1.65 (0.95, 2.84)		0.0732

Analysis performed across trials (pooled analyses and meta-analysis)

The pivotal SC Phase 3 results were compared with the two previous Phase 3 IV studies C1056 and C1057 that supported the approval of IV belimumab 10 mg/kg.

The Phase 3 studies were performed in antibody positive (positive ANA titer ≥ 1:80 and/or anti-dsDNA antibodies ≥ 30 IU/mL) SLE patients with active SLE disease (SELENA SLEDAI ≥ 8 in BEL112341 and SELENA SLEDAI ≥ 6 in C1056 and C1057) who were receiving standard therapy.

Comparison of study populations

In all 3 studies, the majority of subjects were female (93.3%-94.9%) and predominantly White. The mean age of subjects ranged from 35.5 to 40.2 years. Only 1.3%-2.0% of subjects were ≥65 years across the 3 studies. In all 3 Phase 3 studies, the majority of subjects were taking steroids at baseline, although fewer subjects in C1056 (45.9%) were taking prednisone >7.5 mg/day at baseline than in C1057 (69.4%) or BEL112341 (60.2%). The majority of subjects across the studies were taking anti-malarials; more subjects in C1056 were taking immunosuppressants and/or NSAIDs than in C1057 or BEL112341.

Overall, patient demographic and baseline characteristics were similar between BEL112341 and the pooled IV Phase 3 studies. The mean overall SELENA SLEDAI score in BEL112341 was slightly higher (10.4 as compared to 9.7 in the pooled Phase 3 IV trials) which reflects the inclusion criteria (see Table 14).

Table 14: Selected Baseline Disease Characteristics in the Phase 3 Trials

	C1056 - IV				C1057 - IV				BEL112341 - SC		
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	All N = 819	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	All N = 865	Placebo N = 280	200 mg N = 556	All N = 836
SLE Disease duration (yr)											
Mean ± SD[a]	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	6.8 ± 6.83	6.4 ± 6.60	6.5 ± 6.68
BILAG organ domain involvement, n (%)											
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%)	210 (75.0%)	388 (69.8%)	598 (71.5%)
at least 1A	37	38	24	99	52	58	54	164	51	87	138

	C1056 - IV				C1057 - IV				BEL112341 - SC		
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	All N = 819	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	All N = 865	Placebo N = 280	200 mg N = 556	All N = 836
	(13.5%)	(14.0%)	(8.8%)	(12.1%)	(18.1%)	(20.1%)	(18.6%)	(19.0%)	(18.2%)	(15.6%)	(16.5%)
SELENA SLEDAI category, n (%)											
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%)	0	4 (0.7)	4 (0.5)
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%)	112 (40.0)	200 (36.0)	312 (37.3)
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%)	74 (26.4%)	161 (29.0%)	235 (28.1%)
≥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%)	94 (33.6%)	191 (34.4%)	285 (34.1%)
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	10.3 ± 3.04	10.5 ± 3.19	10.4 ± 3.14
SLE flare index[b] , n (%)											
At least 1 flare	82 (29.8%)	63 (23.2%)	59 (21.6%)	204 (24.9%)	57 (19.9%)	53 (18.4%)	56 (19.3%)	166 (19.2%)	57 (20.4%)	92 (16.5%)	149 (17.8%)
PGA category[c], 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%)	19 (6.8%)	40 (7.2%)	59 (7.1%)
>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%)	255 (91.1%)	507 (91.2%)	762 (91.1%)
>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%)	5 (1.8%)	7 (1.3%)	12 (1.4%)
Missing PGA[b]	0	0	0	0	0	0	0	0	1 (0.4)	2 (0.4)	3 (0.4)
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	1.5 ± 0.45	1.6 ± 0.43	1.6 ± 0.44
SLICC Damage Index score											
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	0.7 ± 1.17	0.6 ± 0.99	0.6 ± 1.05
Proteinuria category (g/24 hour), n (%)											
≥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%)	20 (7.1%)	19 (3.4%)	39 (4.7%)
Proteinuria level (g/24 hour)											
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	0.44 ± 0.84	0.39 ± 0.71	0.40 ± 0.75

Source: IV T8, T16; CSR BEL112341 Table 1.14 and Listing 2.2

a. Time elapsed between date of SLE diagnosis and the date of informed consent.
b. Flare index was collected from screening to baseline.
c. In BEL112341, 3 ITT subjects (1 placebo, 2 belimumab) did not have a baseline PGA assessment.

Comparison of efficacy results

Primary endpoint

For the SC Phase 3 study the primary efficacy endpoint of SRI response at Week 52 was statistically significant. The odds of a subject being an SRI responder on belimumab 200 mg SC in BEL112341 was similar to that of a subject being an SRI responder on belimumab 10 mg/kg IV in studies C1056 and C1057 (Table 15).

Table 15: Response at Week 52 in the Phase 3 Trials (dropout = failure)

	C1056 - IV			C1057 - IV			BEL112341 - SC	
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	Placebo N = 279[b]	200 mg N = 554[b]
No.(%) Response	93 (33.8%)	110 (40.6%)	118 (43.2%)	125 (43.6%)	148 (51.4%)	167 (57.6%)	135 (48.4%)	340 (61.4%)
Observed difference vs. placebo (%)	-	6.77	9.41	-	7.83	14.03		12.98
OR (95% CI)[a] 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)		1.68 (1.25, 2.25)
P-value[a]	-	0.1041	0.0207	-	0.0129	0.0006		0.0006

Source: IV T24; CSR BEL112341 Table 2.1

a. For C1056 and C1057, Odds Ratio (95% CI) and p-values were 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 (AIA vs. Other).
For BEL112341, Odds Ratio (95% CI) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

b. Three ITT subjects did not have a baseline PGA assessment and therefore, do not contribute to SRI/component analyses.

An additional (post-hoc) analysis of the IV Phase 3 trials using the same SELENA SLEDAI score cut-off (≥ 8) as the SC study showed a similar (numerically slightly higher) observed difference vs. placebo of 15.6% responders for the 10 mg/kg dose group (OR 1.90; CI: 1.45, 2.50).

Overall, the results for the primary efficacy endpoint of SRI response at Week 52 for study BEL112341 are thus consistent with the Phase 3 IV trials with belimumab administered 10 mg/kg.

Results for belimumab SC and IV (each when compared to placebo) were also consistent in analyses that used higher thresholds of SELENA SLEDAI reduction in calculating the SRI (SRI5-8, see table below), with statistically significant odds ratios in favour of belimumab (Table 16).

Table 16: Response at Week 52 (other sensitivity analyses) in the Phase 3 Trials

	C1056 - IV			C1057 - IV			BEL112341 - SC	
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	Placebo N = 279[a]	200 mg N = 554[a]
SRI5 using SELENA SLEDAI ≥5 point reduction								
Week 52[b]	56 (20.4%)	84 (31.0%)	89 (32.6%)	84 (29.3%)	108 (37.5%)	130 (44.8%)	95 (34.1%)	283 (51.1%)
Odds ratio (95% CI) vs. placebo[c]		1.79 (1.20, 2.67)	1.97 (1.32, 2.94)		1.79 (1.22, 2.62)	2.19 (1.51, 3.18)		2.04 (1.50, 2.78)
P-value[c]		0.0044	0.0009		0.0027	<0.0001		<0.0001
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%)	94 (33.7%)	274 (49.5%)
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)		1.94 (1.43, 2.65)
P-value[c]		0.0066	0.0009		0.0020	<0.0001		<0.0001
SRI7 using SELENA SLEDAI ≥7 point reduction								
Week 52[b]	29 (10.5%)	42 (15.5%)	46 (16.8%)	49 (17.1%)	64 (22.2%)	77 (26.6%)	53 (19.0%)	178 (32.1%)
Odds ratio (95% CI) vs. placebo[c]		1.58 (0.94, 2.67)	1.81 (1.08, 3.04)		1.78 (1.13, 2.81)	1.96 (1.26, 3.04)		2.06 (1.43, 2.96)
P-value[c]		0.0866	0.0250		0.0127	0.0028		0.0001
SRI8 using SELENA SLEDAI ≥8 point reduction								
Week 52[b]	28 (10.2%)	39 (14.4%)	45 (16.5%)	47 (16.4%)	63 (21.9%)	73 (25.2%)	50 (17.9)	174 (31.4%)
Odds ratio (95% CI) vs. placebo[c]		1.51 (0.88, 2.58)	1.86 (1.09, 3.15)		1.86 (1.17, 2.96)	1.91 (1.22, 2.98)		2.15 (1.48, 3.11)
P-value[c]		0.1340	0.0217		0.0083	0.0047		<0.0001

Source: IV TA25.11, TA25.12, TA25.13, TA25.14; CSR BEL112341 Table 2.11, Table 2.12, Table 2.13, Table 2.14

a. Three ITT subjects did not have a baseline PGA assessment and therefore, do not contribute to SRI/component analyses.
b. Premature withdrawal and missing data were handled as described in Section 1.3.5.5.5.
c. For C1056 and C1057, Odds Ratio (95% CI) and p-value were 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 (AIA vs. other).
For BEL112341, Odds Ratio (95% CI) and p-value were from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

Key secondary endpoints

- Time to first severe flare

The proportion of subjects reporting at least 1 severe flare during the study was 18.2% on placebo and 10.6% on belimumab 200 mg SC. This is consistent with the 10 mg/kg findings from C1057 and the pooled IV Phase 3 studies (Table 17).

Table 17: Time to First Severe SFI Flare over 52 Weeks[a] – Modified SLE Flare Index in the Phase 3 Trials

	C1056-IV			C1057-IV			BEL112341-SC	
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	Placebo N = 280	200 mg N = 556
n (%)[b]	67 (24.4)	44 (16.2)	48 (17.6)	66 (23.0)	51 (17.7)	40 (13.8)	51 (18.2)	59 (10.6)
Hazard Ratio (95% CI)[c] vs. placebo	-	0.64 (0.44, 0.94)	0.72 (0.50, 1.05)	-	0.76 (0.52, 1.09)	0.57 (0.39, 0.85)	-	0.51 (0.35, 0.74)
p-value[c]	-	0.0230	0.0867	-	0.1342	0.0055	-	0.0004

Source: IV T57.1; CSR BEL112341 Table 2.22

a. Censored at last available visit at or prior to the Week 52 visit. For subjects who died, data are censored at death if no flares occurred before death. Analysis excludes severe flares that were triggered only by increase in SELENA SLEDAI score to >12.
b. Number (%) of subjects with a severe flare over 52 weeks. Only includes post-baseline severe flares.
c. C1056 and C1057: Hazard ratios and p-values were from Cox proportional hazards model for the comparison between belimumab and placebo adjusting for baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline proteinuria levels (<2 g/24 hour vs. ≥2 g/24 hour equivalent) and race (African descent or indigenous−American descent vs. other). BEL112341: Hazard ratios and p-values were from Cox proportional hazards model for the comparison between belimumab and placebo adjusting for baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

- Percent of subjects with prednisone reduction by ≥25% from baseline to ≤7.5 mg/day during Week 40 through Week 52

Table 18: Reduction by ≥25% from baseline to ≤7.5 mg/day During Week 40 Through Week 52

	C1056-IV			C1057-IV			BEL112341-SC	
	Placebo N = 126	1 mg/kg N = 130	10 mg/kg N = 120	Placebo N = 192	1 mg/kg N= 204	10 mg/kg N = 204	Placebo N =168	200 mg N =335
No.(%) Response[b]	16 (12.7%)	25 (19.2%)	20 (16.7%)	23 (12.0%)	42 (20.6%)	38 (18.6%)	20 (11.9%)	61 (18.2%)
Observed difference vs. Placebo (%)	-	6.53	3.97	-	8.61	6.65		6.30
OR (95% CI)[c] vs. placebo	-	1.57 (0.78, 3.14)	1.26 (0.61, 2.60)	-	1.89 (1.08, 3.31)	1.75 (0.99, 3.08)		1.65 (0.95, 2.84)
p-value[c]	-	0.2034	0.5323	-	0.0252	0.0526		0.0732

Source: IV T59; CSR BEL112341 Table 2.63

a. Includes only subjects with baseline prednisone >7.5 mg/day.
b. Any subject who withdrew from the study prior to the Day 364 (Week 52) visit, missed the Day 364 (Week 52) visit (± 28 day window allowed), and/or received a protocol-prohibited medication or a dose of allowable (but protocol-restricted) medication that resulted in treatment failure designation prior to the Day 364 (Week 52) visit was considered a treatment failure for prednisone reduction.
c. For C1056 and C1057, Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates. For individual studies, the covariates include baseline prednisone level, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline proteinuria level (<2 g/24 hour vs. ≥2 g/24 hour equivalent) and race (AIA vs. other). For BEL112341, Odds Ratio (95% CI) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline prednisone dose, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline complement levels (low C3 and/or C4 vs. no low C3 or C4) and race (Black vs. Other).

The results for study BEL112341 for this key secondary endpoint are consistent with the Phase 3 IV studies.

Selected subgroup analyses

In the Phase 3 IV studies, the subgroup of patients with positive anti-dsDNA and low C3 or C4 was shown to have greater benefit from belimumab treatment than the overall population. In BEL112341, the treatment difference for the SRI response in this subgroup was consistent with that seen in the pooled Phase 3 IV data (Table 19).

For the major secondary endpoint of time to first severe flare, belimumab treatment was superior to placebo in the group with higher disease activity. For the major secondary endpoint of prednisone reduction by ≤25% from baseline to ≤7.5 mg/day during Week 40 through Week 52, there was a trend for more reductions in the belimumab group compared to the placebo group in the high disease activity group, but the difference was not statistically significant.

Table 19: Primary and Major Secondary Endpoints for Subjects with Both Anti-dsDNA ≥30 IU/mL and Low C3 and/or Low C4

Subgroup	Anti-dsDNA positive AND low complement				
	Pooled C1056 + C1057 - IV			BEL112341 - SC	
	Placebo (n=287)	1 mg/kg (n=284)	10 mg/kg (n=305)	Placebo (n=108)	200 mg (n=248)
SRI response rate at Week 52[a]					
n	287	284	305	108	246
Responders, %	31.7	41.5	51.5	47.2	64.6
Observed difference vs. placebo (%)	-	9.8	19.8	-	17.41
OR (95% CI) vs. placebo		1.8 (1.2, 2.5)	2.7 (1.9, 3.9)		2.23 (1.36, 3.64)
p-value	-	0.0020	<0.0001	-	0.0014
Time to First Severe Flare over 52 weeks[b,c]					
n	287	284	305	108	248
Patients experiencing a severe flare (%)	29.6	20.4	19.0	31.5	14.1
Hazard ratio (95% CI)	-	0.67 (0.48, 0.94)	0.61 (0.44, 0.85)	-	0.38 (0.24, 0.61)
p-value	-	0.0203	0.0038	-	<0.0001
Prednisone reduction by ≥25% from baseline to ≤7.5 mg/day during Week 40 through 52[d,e]					
n	173	188	195	70	164
Responders, %	12.1	22.9	18.5	11.4	20.7
Observed difference vs. placebo (%)	-	10.73	6.32	-	9.30
OR (95% CI) vs. placebo		2.02 (1.13, 3.62)	1.55 (0.85, 2.81)		2.08 (0.91, 4.77)
p-value	-	0.0178	0.1510	-	0.0844

Source: CSR BEL112341 Table 2.91, Table 2.23, Table 2.64; IV Table 1.18, Table 1.55, Table 559.

a. For pooled C1056 and C1057, Odds Ratio (95% CI) and p-values were from logistic regression for the comparison between each belimumab dose and placebo with covariates including baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline proteinuria level (<2 g/24 hour vs. ≥2 g/24 hour equivalent), race (AIA vs. Other), and study (C1056 and C1057).
For BEL112341, Odds Ratio (95% CI) and p-value are from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline SELENA SLEDAI score (≤9 vs. ≥10), and race (Black vs. Other).

b. Analysis excludes severe flares that were triggered only by increase in SELENA SLEDAI score to >12. Data censored at last available visit by Week 52 visit. For subjects who died, data are censored at death if no flares indicated before death. Time to first flare is defined as (event date - treatment start date + 1).

c. For pooled C1056 and C1057, Hazard Ratio (95% CI) and p-values were from Cox proportional Hazards model for the comparison between each belimumab dose and placebo adjusted for the baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline proteinuria level (<2 g/24 hour vs. ≥2 g/24 hour equivalent), race (AIA vs. Other), and study (C1056 and C1057).
For BEL112341, Hazard Ratio (95% CI) and p-values were from Cox proportional Hazards model for the comparison between belimumab and placebo adjusted for the baseline SELENA SLEDAI score (≤9 vs. ≥10) and race (Black vs. Other).

d. Includes only subjects with baseline prednisone >7.5 mg/day.

e. For pooled C1056 and C1057, Odds Ratio (95% CI) and p-values were from logistic regression for the comparison between each belimumab dose and placebo with covariates including baseline prednisone dose, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline proteinuria level (<2 g/24 hour vs. ≥2 g/24 hour equivalent), race (AIA vs. Other), and study (C1056 and C1057).

d. For BEL112341, Odds Ratio (95% CI) and p-values from a logistic regression model for the comparison between belimumab and placebo with covariates treatment group, baseline prednisone dose, baseline SELENA SLEDAI score (≤9 vs. ≥10), and race (Black vs. Other).

BEL112341 open-label extension phase

Subjects who completed the double-blind phase of the study could participate in a 6-month open-label extension phase, receiving belimumab 200 mg SC weekly. The first dose was given ~1 week after the last dose of the double-blind phase, i.e., at Week 52. Participating subjects continued to be monitored for safety and, at a reduced frequency, efficacy. More latitude was permitted for changes in background medication during the extension phase. For analysis of the open-label phase, baseline for both treatment groups was defined as the last pre-belimumab assessment. Thus, for the belimumab 200 mg SC group, baseline was Day 0 of the double-blind phase and for the placebo to belimumab 200 mg SC group, baseline was the Week 52 assessment.

A total of 662 out of the 677 subjects that completed the double-blind part of the study were enrolled and received at least one dose of belimumab 200 mg SC during open label. Of these, 206 subjects switched from placebo during the double-blind phase to belimumab 200 mg SC and 456 subjects had received belimumab 200 mg SC for 52 weeks during the double-blind phase continued to receive belimumab during the open-label phase.

The percentage of SRI responders during the open-label phase at open-label Week 24/Exit was 16.1% for subjects in the placebo to belimumab 200 mg group and 76.3% for subjects in the belimumab 200 mg SC group. However, the different duration of exposure to belimumab and definition of baseline between the groups should be considered. No statistical testing was performed for the open-label phase data.

Clinical studies in special populations

No studies in the paediatric population have been performed with belimumab until now.

Based on PK data and subgroup analyses in study BEL112341, no dose adjustment is recommended for elderly patients or with respect to gender, race and ethnicity, body weight, renal impairment, hepatic function, or disease state, consistent with the IV formulation.

No specific clinical studies have been performed in elderly.

Supportive studies

Study 200339 (real-life use of autoinjector device)

Study 200339 was an open-label, single-arm; multi-dose study of belimumab (200 mg) administered SC via an autoinjector in subjects with SLE who had previously received belimumab. The study was designed to assess the suitability of an autoinjector for self-administration of belimumab. Other objectives were to evaluate injection failures related to use (use errors) or device performance (device errors), the safety and tolerability of belimumab administered via the autoinjector, and to characterize the change in belimumab trough concentrations when switching from IV to SC administration.

SLE patients switching from 10 mg/kg IV every 4 weeks to 200 mg SC every week used a 1 to 4 week interval between the first SC dose and the last IV dose. Eligible subjects self-administered belimumab SC (200 mg/mL formulation) into the thigh or abdomen using the autoinjector for 8 weekly doses starting at Day 0; 4 doses were administered under observation in the clinic and 4 were administered outside the clinic and without observation.

A total of 95 subjects were enrolled. Ninety subjects administered the first 2 injections in the study and 87 administered their drug at home through Week 7. A high proportion (89/90: 99%) of subjects had successful injections in their observed first and second doses using the autoinjector in Weeks 1 and 2.

A high proportion of subjects were also able to successfully self-administer their observed dose of belimumab 200 mg SC using the autoinjector at Weeks 4 and 8 (85/87: 98%) and outside the clinic setting at Weeks 3, 5, 6, and 7 (81/87: 93%). Over the 8-week treatment period, a total of 736 once weekly injections were attempted and 720 (98%) injections were concluded to be successful.

The median of belimumab serum concentration at Week 8 was 113 µg/mL, indicating that the average steady-state exposure for weekly 200 mg belimumab SC was similar to the Cavg of 110 µg/mL for 10 mg/kg belimumab IV every 4 weeks.

For switching intervals between 2 and 4 weeks, median Week 8 to Week 1 differences in belimumab concentrations were close to zero, i.e., subjects were most likely to start close to their steady-state belimumab level when switched from IV to SC with a 2-4 week time interval. On the other hand, the median % changes between Week 8 and Week 1 in belimumab trough concentration was more than 50% for switching intervals of ≤1.5 weeks.

Human factor validation reports TR-06-15-009 (autoinjector) and TR-06-15-008 (safety syringe)

Both studies included a total of 30 participants divided into two user groups including (1) 15 SLE patients who received representative training on how to use the device representing the high-risk intended user population for this device considering their physical symptoms and lack of experience using such devices to self-administer subcutaneous injections and (2) 15 healthcare providers (HCPs) who self-trained by using the materials provided in the representative product pack.

In both studies, all participants (30/30, 100%) successfully prepared and carried out the full injection procedure. There were no patterns of (preventable) failures or use errors observed. The results of these studies indicate a reliable usability of the devices (commercial prefilled syringe and autoinjector) and label comprehension by representative users under realistic conditions.

2.5.3. Discussion on clinical efficacy

The MAH has developed a belimumab SC formulation for the same indication as approved for the IV formulation, i.e. as add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity. The product was developed as an alternative to the IV formulation as some physicians and patients may have a preference for an SC option.

Design and conduct of clinical studies

The MAH conducted a single pivotal Phase 3 randomized double-blind placebo-controlled 52 week trial (BEL 112341) to support the SC formulation. For the most part, the critical design elements of this SC study were the same as those utilized for the previous pivotal Phase 3 IV program.

A few adaptations were made, including the use of raised entry criteria for the SELENA SLEDAI score at screening from ≥ 6 to≥ 8. This change was made based on the results from the IV studies which showed that patients with higher disease activity, as reflected by a higher SELENA SLEDAI score, were more likely to respond to belimumab. This change is considered acceptable. The primary efficacy endpoint, SRI response rate at Week 52, is unchanged from the previous pivotal Phase 3 studies. Other differences included removal of male subject contraception requirements and allowing previous use of IV cyclophosphamide within 3 months prior to Day 0 instead of 6 months. Also, subjects with evidence of serious suicide risk were specifically excluded in the SC study. This stipulation was considered to facilitate the assessment of the impact of belimumab, if any, on serious psychiatric events.

The fixed dose of the SC formulation, 200 mg administered once weekly is targeting a similar overall exposure in terms of AUC at steady state as compared with monthly IV dosing of 10 mg/kg. This approach is considered as reasonable under the assumption that overall exposure is a good predictor of efficacy.

Overall, the design of study BEL112341 for the purpose of characterising the efficacy and safety of belimumab SC in adult patients with SLE supported by the previously conducted studies with the IV formulation is considered acceptable.

The final commercial device formats (autoinjector and safety syringe) were not included in the pivotal Phase 3 trial. The device bridging program included laboratory based performance testing, human factors studies and clinical studies (autoinjector only). Study BEL117100 assessed the relative bioavailability of a single dose of SC belimumab formulation 06-D for the autoinjector and the prefilled syringe in healthy volunteers. In addition, usability and reliability of the autoinjector device with respect to chronic real-life use by adult subjects with SLE were evaluated in Study 200339.

Efficacy data and additional analyses

BEL112341 showed that belimumab 200 mg CS in addition to standard therapy achieved a greater proportion of SRI responders at Week 52 compared to placebo plus standard therapy (48.4% placebo, 61.4% belimumab, p=0.0006). These results were in line with the underlying assumptions of the study. The odds of a subject being an SRI responder on SC belimumab (odds ratio [OR] 1.68; 95% CI: 1.25. 2.25; p=0.0006) was similar to that of a subject being an SRI responder in the pooled IV studies using belimumab 10 mg/kg (OR 1.68; 95% CI: 1.32, 2.15; p<0.0001).

Belimumab also demonstrated efficacy in each of the components of the SRI (≥ 4 point reduction in SELENA SLEDAI score over baseline, no worsening in PGA (<0.3 point increase over baseline, no new BILAG 1A or 2B scores) (all p<0.05). The prespecified sensitivity analyses of the primary SRI endpoint were all statistically significant, consistent with the primary results. This included analyses that used a 5 to 8 point difference in the SELENA SLEDAI score in the SRI (SRI5 to SRI8).

In an additional modified analysis replacing the" No New BILAG 1A/2B domain score" component with "No BILAG 1A/2B domain score" the treatment difference remained significant in BEL112341 (OR 1.62; 95% CI: 1.20, 2.17; p=0.0014).

The differences in SRI response rate observed between the belimumab and placebo groups were numerically superior by Week 8, with statistical significance obtained by Week 16 and sustained through Week 52. To compare, in C1057 and the pooled C1056 and C1057 analyses, the differences in SRI response were statistically significant at Week 16 and from Week 24 to Week 52 for the 10 mg/kg group. In C1056 the difference was statistically significant at Week 52, but not earlier.

As the first major secondary endpoint, belimumab reduced the risk of subjects experiencing at least 1 severe flare by 49% (hazard ratio [HR] 0.51; 95% CI: 0.35, 0.74; p=0.0004). The second major endpoint, conducted in the subgroup of subjects who were receiving >7.5 mg/day of prednisone at baseline, showed a numerically higher proportion of subjects reduced their steroid dose by ≥ 25% to ≤ 7.5 mg/day during Weeks 40 to 52 compared to placebo subjects; the difference approached statistical significance. The results for these endpoints were consistent with the IV program.

In BEL112341, subjects were required to have a SELENA SLEDAI score of ≥ 8 at screening. In total 773 of 836 (92.5%) of subjects had this score at baseline. The response rate in this subgroup was similar to the overall study population (difference vs. placebo 13.25%, odds ratio 1.72; 95% CI: 1.26, 2.34; p=0.0006). Given that the SELENA SLEDAI inclusion criterion was slightly different from the IV

program, a post-hoc analysis was conducted of this same subgroup (baseline SELENA SLEDAI score ≥ 8) in the IV Phase 3 trials which showed a (numerically slightly higher) observed difference vs. placebo of 15.6% responders for the 10 mg/kg dose group (OR 1.90; CI: 1.45, 2.50).

SRI analysis was performed using 3 definitions of high disease activity: a SELENA SLEDAI score of ≥ 10, low C3 and/or low C4, and the combination of anti-dsDNA positivity and low complement. Analysis of the major secondary endpoints was also performed for those subjects with both anti-dsDNA positivity and low complement. Consistent with the IV program, a more robust effect of belimumab treatment was observed in subjects with higher levels of disease activity.

Subjects with low complement and positive anti-dsDNA demonstrated a treatment difference for belimumab relative to placebo of 17.41% more responders (odds ratio 2.23; 95% CI: 1.36, 3.64; p=0.0014) (as compared to a delta of 9.64 for the not low complement/anti-dsDNA subgroup and 12.98 for the overall population). This subgroup also showed a more pronounced effect on prevention of severe flare with 62% reduced risk of severe flare compared to placebo (HR 0.38; p <0.0001). The other major secondary endpoint relating to prednisone reduction did not reach statistical significance ((20.7% vs. 11.4%; p=0.0844).

At baseline in BEL112341, 147 subjects (17.6%) had proteinuria >0.5g/24. In this subgroup, the percentage of subjects with renal flares was also decreased in this subgroup in the belimumab group compared to placebo with 11.1% of belimumab subjects with proteinuria at baseline experiencing a renal flare, compared to 27.1% of placebo subjects with proteinuria at baseline (HR 0.40; 95% CI: 0.18, 0.90; p=0.0272).

Belimumab SC 200 mg fixed dosing dose represent a lower dosing regimen for those with higher body weight compared with IV dosing at 10 mg/kg. However, the efficacy of belimumab 200 mg SC fixed dosing was not negatively impacted by increasing body weight.

In some regions, including Western and Eastern Europe, as well as Asia, the observed difference in SRI response vs. placebo was numerically lower (ranging from 7.6 to 9.2%) and not statistically significant. Overall, however, the results from study BEL112341 appear to be consistent with the efficacy demonstrated in the IV Phase 3 registration program (studies C1056 and C1057).

The devices intended planned for commercial use (the autoinjector and prefilled syringe with needle guard) were not utilized in the Phase 3 study but employ the same prefilled syringe as primary drug container closure as was used in the Phase 3 study. As part of the device bridging program, the usability and reliability of the autoinjector device with respect to chronic real-life use by adult subjects with SLE were evaluated. Likewise, a human factors validation studies were conducted to demonstrate reliable usability of the devices (commercial prefilled syringe and autoinjector) and label comprehension by representative users under realistic conditions. The results from these studies were considered as supportive.

2.5.4. Conclusions on the clinical efficacy

The results from the belimumab SC Phase 3 trial, BEL112341, combined with the previous belimumab IV Phase 3 program demonstrate the efficacy for belimumab 200 mg SC as an add-on treatment to standard therapy for the indicated population, i.e. adult patients with active autoantibody-positive SLE with a high degree of disease activity despite standard therapy.

The CHMP considers the application approvable from a clinical efficacy point of view.

2.6. Clinical safety

The primary safety population for belimumab SC is comprised of the subjects from study BEL112341.

The primary safety population of the supporting IV program was comprised of subjects from the Phase 2 study LBSL02 and the 2 Phase 3 studies C1056 and C1057 (all together, the CRD studies).

Patient exposure

In the SC BEL112341 study 836 subjects participated, of whom 556 (66.5%) received belimumab. The primary safety population for the IV formulation includes 2133 subjects of whom 68.4% (1458/2133) were administered belimumab.

Adverse events

The adverse events are summarised in the Table 20.

Table 20: Adverse Event Summary (ITT Population, CRD Studies)

	Number (%) of Subjects					
	C1056/C1057/LBSL02 Pooled IV		BEL112341-SC		Pooled IV + SC	
Subjects with at least one:	Placebo IV (N=675)	BEL IV (N=1458)	Placebo SC (N=280)	BEL SC 200 mg (N=556)	Placebo IV + Placebo SC (N=955)	BEL IV + BEL SC 200 mg (N=2014)
AE	623 (92.3)	1354 (92.9)	236 (84.3)	449 (80.8)	859 (89.9)	1803 (89.5)
Related AE	282 (41.8)	586 (40.2)	73 (26.1)	173 (31.1)	355 (37.2)	759 (37.7)
Serious AE	103 (15.3)	248 (17.0)	44 (15.7)	60 (10.8)	147 (15.4)	308 (15.3)
Severe[a] AE	99 (14.7)	220 (15.1)	40 (14.3)	55 (9.9)	139 (14.6)	275 (13.7)
Serious and/or severe[a] AE	138 (20.4)	328 (22.5)	59 (21.1)	82 (14.7)	197 (20.6)	410 (20.4)
AE resulting in study agent discontinuation	48 (7.1)	88 (6.0)	25 (8.9)	40 (7.2)	73 (7.6)	128 (6.4)
Death	3 (0.4)	11 (0.8)	2 (0.7)	3 (0.5)	5 (0.5)	14 (0.7)

Source: CRD Table 2.1 Note: Only treatment-emergent AEs are summarized. MedDRA version 17.1

a. Severe or life threatening.

Common adverse events

Treatment-emergent AEs by SOC for the CRD studies are summarized in Table 21.

Table 21: Adverse Events by System Organ Class (ITT Population, CRD Studies)

	Number (%) of Subjects					
	C1056/C1057/LBSL02 Pooled IV		BEL112341-SC		Pooled IV + SC	
System Organ Class	Placebo IV (N=675)	BEL IV (N=1458)	Placebo SC (N=280)	BEL SC 200 mg (N=556)	Placebo IV + Placebo SC (N=955)	BEL IV + BEL SC 200 mg (N=2014)
Any event	623 (92.3)	1354 (92.9)	236 (84.3)	449 (80.8)	859 (89.9)	1803 (89.5)

System Organ Class	Number (%) of Subjects					
	C1056/C1057/LBSL02 Pooled IV		BEL112341-SC		Pooled IV + SC	
	Placebo IV (N=675)	BEL IV (N=1458)	Placebo SC (N=280)	BEL SC 200 mg (N=556)	Placebo IV + Placebo SC (N=955)	BEL IV + BEL SC 200 mg (N=2014)
Infections and infestations	444 (65.8)	1035 (71.0)	159 (56.8)	308 (55.4)	603 (63.1)	1343 (66.7)
Musculoskeletal and connective tissue disorders	305 (45.2)	638 (43.8)	66 (23.6)	124 (22.3)	371 (38.8)	762 (37.8)
Gastrointestinal disorders	260 (38.5)	597 (40.9)	68 (24.3)	125 (22.5)	328 (34.3)	722 (35.8)
Nervous system disorders	235 (34.8)	525 (36.0)	53 (18.9)	111 (20.0)	288 (30.2)	636 (31.6)
Skin and subcutaneous tissue disorders	233 (34.5)	543 (37.2)	60 (21.4)	80 (14.4)	293 (30.7)	623 (30.9)
General disorders and administration site conditions	196 (29.0)	446 (30.6)	43 (15.4)	96 (17.3)	239 (25.0)	542 (26.9)
Respiratory, thoracic and mediastinal disorders	176 (26.1)	366 (25.1)	48 (17.1)	81 (14.6)	224 (23.5)	447 (22.2)
Injury, poisoning and procedural complications	115 (17.0)	288 (19.8)	35 (12.5)	56 (10.1)	150 (15.7)	344 (17.1)
Investigations	101 (15.0)	227 (15.6)	34 (12.1)	58 (10.4)	135 (14.1)	285 (14.2)
Vascular disorders	102 (15.1)	211 (14.5)	28 (10.0)	43 (7.7)	130 (13.6)	254 (12.6)
Psychiatric disorders	80 (11.9)	219 (15.0)	32 (11.4)	35 (6.3)	112 (11.7)	254 (12.6)
Blood and lymphatic system disorders	90 (13.3)	190 (13.0)	24 (8.6)	53 (9.5)	114 (11.9)	243 (12.1)
Renal and urinary disorders	77 (11.4)	143 (9.8)	25 (8.9)	38 (6.8)	102 (10.7)	181 (9.0)
Metabolism and nutrition disorders	66 (9.8)	156 (10.7)	21 (7.5)	32 (5.8)	87 (9.1)	188 (9.3)
Reproductive system and breast disorders	65 (9.6)	149 (10.2)	18 (6.4)	42 (7.6)	83 (8.7)	191 (9.5)
Eye disorders	52 (7.7)	148 (10.2)	21 (7.5)	37 (6.7)	73 (7.6)	185 (9.2)
Cardiac disorders	44 (6.5)	110 (7.5)	7 (2.5)	16 (2.9)	51 (5.3)	126 (6.3)
Ear and labyrinth disorders	33 (4.9)	78 (5.3)	7 (2.5)	13 (2.3)	40 (4.2)	91 (4.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (3.3)	42 (2.9)	9 (3.2)	15 (2.7)	31 (3.2)	57 (2.8)
Immune system disorders	21 (3.1)	52 (3.6)	4 (1.4)	9 (1.6)	25 (2.6)	61 (3.0)

System Organ Class	Number (%) of Subjects					
	C1056/C1057/LBSL02 Pooled IV		BEL112341-SC		Pooled IV + SC	
	Placebo IV (N=675)	BEL IV (N=1458)	Placebo SC (N=280)	BEL SC 200 mg (N=556)	Placebo IV + Placebo SC (N=955)	BEL IV + BEL SC 200 mg (N=2014)
Hepatobiliary disorders	18 (2.7)	34 (2.3)	3 (1.1)	8 (1.4)	21 (2.2)	42 (2.1)
Endocrine disorders	9 (1.3)	29 (2.0)	3 (1.1)	8 (1.4)	12 (1.3)	37 (1.8)
Surgical and medical procedures	13 (1.9)	33 (2.3)	0	0	13 (1.4)	33 (1.6)
Pregnancy, puerperium and perinatal conditions	4 (0.6)	8 (0.5)	0	2 (0.4)	4 (0.4)	10 (0.5)
Congenital, familial and genetic disorders	2 (0.3)	4 (0.3)	0	0	2 (0.2)	4 (0.2)
Social circumstances	0	2 (0.1)	0	0	0	2 (<0.1)

Source: CRD Table 2.2
Note: Subjects only counted once per SOC. Only treatment-emergent AEs are summarized.
MedDRA version 17.1

The incidence of AEs by SOC was generally similar for the belimumab SC group compared to placebo. As also shown in Table 21, the incidence of AEs reporting for both active and placebo tended to be lower in the SC study as compared to the pooled IV studies.

In study BEL112341, common treatment-emergent AE PTs were headache (9.3% placebo, 10.3% belimumab 200 mg SC), urinary tract infection bacterial (6.4% placebo, 7.6% belimumab), and arthralgia (3.9% placebo, 5.8% belimumab) were reported more frequently for belimumab and at least 1% greater incidence than for placebo. Frequent AEs that occurred more commonly in the placebo group and at least 1% greater incidence than belimumab were nasopharyngitis (7.9% placebo, 6.8% belimumab), nausea (7.9% placebo, 6.8% belimumab), cough (6.8% placebo, 4.0% belimumab), and insomnia (7.1% placebo, 3.2% belimumab).

The incidence of AEs considered by the investigator to be at least possibly related to study agent in study BEL112341 was 26% for the placebo group and 31% for the belimumab 200 mg SC group. The SOC with the highest incidence of drug-related AEs overall was infections and infestations (19% placebo, 19% belimumab). The PT with the highest incidence of drug-related AEs overall was herpes zoster (3.2% placebo, 2.2% belimumab). Incidences in the belimumab group were similar to or lower than those in the placebo group for the majority of drug related AEs.

The majority of AEs in study BEL112341 were mild or moderate in severity. The incidence of severe (including life-threatening) AEs in the placebo group was 14.3% compared with 9.9% in the belimumab group.

No ADA positive subjects

Local SC injection site reactions

Local injection site reactions occurred in 2.5% and 6.1% of subjects in the placebo and belimumab 200 mg SC groups, respectively. All local injection site reactions were mild or moderate in severity, and no serious local injection site events were reported. There were 64 events of local injection site reactions in 34 belimumab-treated subjects as compared to 12 events in 7 placebo-treated patients during the double-blind phase of the study. The first appearance of local reactions was reported somewhat more frequently during the two injections of belimumab (in 11 subjects in total) but they also occurred during later phases of the study. Most local site injection reactions started on the day the injection was administered and almost all events resolved. (Table 22)

Two subjects in the belimumab group discontinued due to a local injection site reaction. Subject discontinued due to injection site induration (moderate, definitely related) that occurred 3 days after receiving the second dose of belimumab, and Subject discontinued due to injection site erythema (mild, probably related) that began 4 days after receiving the second dose of belimumab.

Table 22: Injection Site Reactions Occurring in ≥0.5% of Subjects in Either Treatment Group (Double-Blind Phase) (ITT Population, Study BEL112341)

Preferred Term[a]	Number (%) of Subjects[b]	
	Placebo N=280	Belimumab 200 mg N=556
Any Event	7 (2.5)	34 (6.1)
Injection site pain	1 (0.4)	10 (1.8)
Injection site haematoma	2 (0.7)	8 (1.4)
Injection site erythema	0	9 (1.6)
Injection site pruritus	1 (0.4)	4 (0.7)
Injection site induration	1 (0.4)	3 (0.5)

Source: CSR BEL112341, Table 103.90

a. AEs are presented in descending order from the MedDRA preferred term with the highest overall incidence. If the overall incidences for any two or more adverse event preferred terms are equal, the events are presented in alphabetical order.

b. Subjects are only counted once per preferred term.

AEs of special interest

- *Post-Injection/Infusion Systemic Reactions*

In study BEL112341, the incidences of post-injection systemic reactions in the belimumab 200 mg SC group were lower than or similar to that in the placebo group for each category.

The incidences of post injection systemic reactions per anaphylactic reaction custom MedDRA query (CMQ) broad search were 8.6% in the placebo and 6.8% in the belimumab groups.

For post injection systemic reactions per anaphylactic reaction custom MedDRA query (CMQ) broad search that were serious, the incidence in the placebo group and the belimumab group was 0 and 0.2%, respectively. Serious delayed non-acute hypersensitivity reactions per sponsor adjudication were low in both treatment groups (0.4% placebo, 0 belimumab). No serious anaphylaxis per Sampson criteria, serious acute post injection systemic reactions, serious acute hypersensitivity reactions, or serious delayed acute hypersensitivity reactions occurred.

Table 23: Post-Injection/Infusion Systemic Reactions AESI Interest by Category (ITT Population, CRD Studies)

	Number (%) of Subjects					
	C1056/C1057/LBSL02 Pooled IV		BEL112341-SC		Pooled IV + SC	
	Placebo	BEL IV	Placebo	BEL	Placebo	BEL IV +

	IV (N=675)	(N=1458)	SC (N=280)	SC 200 mg (N=556)	IV+ Placebo SC (N=955)	BEL SC 200 mg (N=2014)
Post-Injection/Infusion Systemic Reactions	65 (9.6)	198 (13.6)	25 (8.9)	38 (6.8)	90 (9.4)	236 (11.7)
Post-Injection/Infusion Systemic Reactions per Anaphylactic Reaction CMQ narrow search[a]	7 (1.0)	29 (2.0)	1 (0.4)	2 (0.4)	8 (0.8)	31 (1.5)
Post-Injection/Infusion Systemic Reactions per Anaphylactic Reaction CMQ broad search[a]	65 (9.6)	198 (13.6)	24 (8.6)	38 (6.8)	89 (9.3)	236 (11.7)
Post-Injection/Infusion Systemic Reactions per Anaphylactic Reaction CMQ algorithmic search[a]	10 (1.5)	31 (2.1)	1 (0.4)	2 (0.4)	11 (1.2)	33 (1.6)
Serious Anaphylaxis per Sampson Criteria[b]	0	4 (0.3)	0	0	0	4 (0.2)
Serious Acute Post-Injection/Infusion Systemic Reactions/ Hypersensitivity per GSK adjudication[b,c]	2 (0.3)	12 (0.8)	0	0	2 (0.2)	12 (0.6)
Serious Acute Post-Injection/Infusion Systemic Reactions Excluding Hypersensitivity per GSK adjudication[b,c]	2 (0.3)	5 (0.3)	0	0	2 (0.2)	5 (0.2)
Serious Acute Hypersensitivity Reactions per GSK adjudication[b,c]	0	7 (0.5)	0	0	0	7 (0.3)
Serious Delayed Acute Hypersensitivity Reactions per GSK adjudication[b,c]	0	0	0	0	0	0
Serious Delayed Non-Acute Hypersensitivity Reactions per GSK adjudication[b,c]	0	0	1 (0.4)	0	1 (0.1)	0

Source: CRD Table 2.21

Note: Subjects only counted once per category. Only treatment-emergent AEs are summarized. MedDRA version 17.1

a. Per Custom MedDRA query.

b. Per sponsor adjudication.

c. Acute = Onset ≤ 1 day; Delayed Acute = Onset 2-3 days; Delayed Non-Acute = Onset 4-21 days.

Table 24: Post-Injection Systemic Reactions per Anaphylactic Reactions CMQ Broad Search during the First 6 Injections (Double-Blind Phase) (ITT Population)

Treatment Group	Number (%) of Subjects					
	Injection Number					
	1	2	3	4	5	6
Placebo, N	280	276	273	273	273	272
	1 (0.4)	1 (0.4)	0	0	1 (0.4)	3 (1.1)
Belimumab 200 mg SC, N	556	553	549	548	546	545
	5 (0.9)	2 (0.4)	2 (0.4)	5 (0.9)	0	1 (0.2)

There were slightly more cases in the belimumab group over the course of the first 6 injections but no obvious differences between the groups. No premedication was required as part of the study drug treatment regimen during the study and none is recommended in the SmPC for the SC formulation.

Three subjects were withdrawn from study treatment with belimumab as a result of systemic reaction events. One subject in the SC belimumab group was discontinued from study BEL112341 due to swelling face, lip swelling, and anaphylactic reaction (all moderate, possibly related) that occurred 1 day after receiving the first dose of belimumab; the subject was not premedicated prior to injection and was subsequently treated with depo-medrol 80 mg and celestone soluspan 30 mg. The subject already was being treated with steroids as concomitant medication. The patient had a history of skin photosensitivity but no reported history of (systemic) allergic reactions. Subject eported severe allergic pruritis and urticaria that started on the day of the first injection and resolved after 3 days. Belimumab was considered probably related and was withdrawn as a result of these events. Subject developed multiple rashes of mild severity 2 days after the fourth dose that resolved after 7 days. Belimumab was considered probably not related but was nevertheless withdrawn as a result of the events.

- *Infections including opportunistic infections*

In study BEL112341, the incidence of AESI infections was lower among the belimumab SC treated subjects (5.4%) than that observed among the placebo-treated subjects (7.5%). The incidence of serious AESI was 1.4% for belimumab as compared to 1.1% for the placebo group.

There were 2 serious opportunistic infections in the belimumab 200 mg group (2/556 [0.4%], namely TB and Candida, extra-oral/esophageal (per GSK adjudication) and none in placebo.

- *Malignant neoplasms*

Malignancies reported during the double-blind phase of study BEL112341 consisted solely of solid tumors, which occurred in 0.4% of subjects in each treatment group. The PTs for the 2 solid tumors reported in the belimumab group were endometrial cancer (0.2%) and intraductal proliferative breast lesion (0.2%), and the solid tumor reported for the placebo group was breast cancer (0.4%).

- *Depression/ suicide/self-injury*

In study BEL112341, suicidality was assessed at every visit using the Columbia-Suicide Severity Rating Scale (C-SSRS). There were no events reported in the placebo group and 3 subjects with treatment emergent suicidal ideations per the C-SSRS in the belimumab 200 mg SC group (2 events were in ideation category 3 of “Active suicidal ideation with any methods (not plan) without intent to act” and 1 in ideation category 1 of “Non-specific active suicidal thoughts.” No behavior events were reported.

The incidence of depression AESI per CMQ was 3.6% in the placebo group and 2.7% in the belimumab 200 mg SC group.

Safety findings from the BEL112341 open-label extension phase

The incidence of subjects experiencing at least 1 AE during the open-label phase was 49.2% and similar between the groups. The most frequent (≥3% in any treatment group) treatment-emergent AEs were viral upper respiratory tract infection, arthralgia, urinary tract infection bacterial, and nasopharyngitis. No treatment-emergent AEs were reported in ≥5% of subjects in either treatment group.

Overall, local injection site reactions occurred in 1.5% and 0.2% of subjects in the placebo to belimumab 200 mg SC and belimumab 200 mg SC groups, respectively. During the open-label phase, all local injection site reactions were mild in severity.

Post-injection systemic reactions occurred in 4.4% and 2.6% of subjects in the placebo to belimumab 200 mg SC and belimumab 200 mg SC groups, respectively. A total of 4 (0.6%) subjects had serious post-injection systemic reactions per anaphylactic reaction customized MedDRA query (CMQ) broad search during the open-label phase, 1 (0.5%) subject in the placebo to belimumab 200 mg SC group and 3 (0.7%) subjects in the belimumab 200 mg SC group.

Regarding other AESI, no subjects had a malignant neoplasm AESI during the open-label phase. Infection AESI occurred in 3.4% and 2.2% of subjects in the placebo to belimumab 200 mg SC and belimumab 200 mg SC groups, respectively. Serious infections included one subject with herpes zoster and one with mycobacterial infection in the placebo to belimumab 200 mg SC group and one case each of staphylococcal sepsis and tuberculosis in the belimumab 200 mg SC continuation group. Rates of depression/suicide/self-injury event AESIs were similar between the groups (1.8% overall).

In the double-blind phase of study BEL112341, no subject had tested positive for immunogenicity following belimumab 200 mg SC administration. Three subjects tested positive following belimumab 200 mg SC administration during the open-label phase or at the 8-Week Follow-up visit. All 3 of these subjects had negative values on subsequent follow-up testing.

Overall, the data from the open-label phase of study BEL112341 did not evoke any new safety concerns.

Safety findings from other studies

Study 2003339

Study 200339 was a Phase 2 real-life use study of belimumab 200 mg administered SC weekly for 8 weeks to subjects with SLE using the autoinjector (formulation 06-D, 200 mg/mL).

A total of 95 subjects were enrolled and treated with at least 1 dose of belimumab 200 mg SC and were included in the ITT population. Of these subjects, 91 (96%) subjects completed the study and 4 (4%) subjects prematurely withdrew from the study. The reason for withdrawal was due to an AE for 3 of these 4 subjects. A total of 93 (98%) subjects had received previous belimumab IV treatment and 2 (2%) subjects received previous belimumab SC treatment prior to enrolling into the study. A total of 90 (95%) subjects resumed or started belimumab IV treatment after the study. The most common AE SOCs (≥5% of subjects) were infections and infestations (19%), musculoskeletal and connective tissue disorders (13%), general disorders and administration site conditions (11%), and gastrointestinal disorders (9%).

Treatment-emergent AEs reported in more than 2 subjects were nausea (6%), arthralgia (4%), and bronchitis, sinusitis, diarrhea, systemic lupus erythematosus (all 3%). A total of 2 (2%) subjects had a treatment-emergent infection AESI during the study. Herpes zoster AESI were reported in 2 (2%) subjects. One (1%) subject had a herpes zoster AESI that led to discontinuation of study agent.

Overall, a total of 3 (3%) subjects had treatment-emergent AEs that led to discontinuation of belimumab 200 mg SC during the study: 1 subject or an SAE of postoperative abscess; 1 subject for AEs of nausea, vomiting and pyrexia; and 1 subject or the AE of herpes zoster.

Long-term continuation studies (belimumab IV)

In the initial submission, data (interim reporting) from 3 repeat-dose long term studies of belimumab IV in subjects with SLE, BEL112626, BEL112233, and BEL112234, were integrated for long term continuation (LTC) safety analyses (DLP of 08 September 2014). SAE data from the ongoing LTC studies (BEL112234 and BEL112626) from 09 September 2014 to 08 March 2016 were also presented.

Additional SAE data with a cut-off date of 22 October 2016 was provided as part of the Day 120 LoQ response.

Overall, the LTC data including the additional SAE data did not evoke any new safety concerns.

Serious adverse event / deaths / other significant events

In study BEL112341, a total of 5 deaths occurred in the double-blind phase of the study, 2 (0.7%) in the placebo group and 3 (0.5%) in the belimumab 200 mg SC group. The 3 deaths in the belimumab group were due to infection and the 2 deaths in the placebo group were cardiac arrest and thrombocytopenia.

Table 25: Listing of Deaths in the Double-Blind Phase of Study BEL112341 (Randomized Population)

Treatment Group	Preferred Term	Relation to Study Agent	Days Since First/Last Dose
Placebo	Cardiac arrest	Not Related	159/18
	Thrombocytopenia	Not Related	175/6
Belimumab 200 mg SC	Tuberculosis of central nervous system	Possibly Related	176/7
	Urosepsis	Possibly Related	142/15
	Bacterial sepsis	Probably Not Related	375/38

One additional subject in the belimumab group died off study of Grade 4 life threatening sepsis 143 days after her last dose of belimumab. The subject had withdrawn from the study on Day 28 due to the AE of mild, non-serious injection site erythema considered related to study agent. The subject had been admitted to hospital 125 days after the last dose of belimumab due to haemorrhagic shock secondary to bleeding esophageal varices.

In study BEL112341, SAEs were reported for approximately 16% and 11% of subjects in the placebo and belimumab 200 mg SC groups, respectively. The SOC with the highest incidence of SAEs overall was infections and infestations (5.4% placebo, 4.1% belimumab). The incidence of AEs by SOC was generally similar for the belimumab SC group compared to placebo.

By PT, the only SAE reported for >1% of subjects in either treatment group was thrombocytopenia (1.1% placebo, 0 belimumab). SAEs reported in >0.5% of subjects in either treatment group were cellulitis, pneumonia, pneumonia bacterial, renal failure acute, thrombocytopenia, dysphagia, headache, lupus vasculitis, and nephrotic syndrome. No trends of concern were observed.

During the open-label phase of the study BEL112341 two (0.3%) subjects died (table 26):

Table 26: Listing of Deaths in the Open-Label Phase of Study BEL112341 (ITT population)

Treatment Group	Preferred Term	Relation to Study Agent	Days Since First Active Dose/ Days Since Last Dose
Placebo to Belimumab 200 mg	Metabolic acidosis[a]	Not related	31/30
Belimumab 200 mg to Belimumab 200 mg	Acute respiratory failure[b]	Not related	395/2

Source: Listing 13.4 and Listing 13.5

a. This subject also had non-fatal SAEs of deep vein thrombosis, antiphospholipid syndrome, and acute kidney injury 31 days after the first active dose of belimumab.
b. This subject also had a non-fatal SAE of pneumonia 393 days after the first active dose of belimumab.

1 death in the placebo to belimumab 200 mg SC group was due to metabolic acidosis following events of antiphospolipid syndrome, acute kidney injury and deep vein thrombosis. One death in the belimumab 200 mg SC group was an infection-related death due to pneumonia and acute respiratory failure due to an SAE of community-acquired pneumonia 393 days after the first dose of belimumab. The reported cause of death was acute respiratory failure, considered unrelated to belimumab by the investigator. However, a causal relationship to the infection cannot be excluded.

SAEs were reported for 5.9% of subjects (6.8% placebo to belimumab 200 mg SC, 5.5% belimumab 200 mg SC) during the open-label phase with no meaningful differences between the groups. The overall incidence of AEs leading to discontinuation of study agent during the open-label phase was 2.6% for all subjects (2.4% placebo to belimumab 200 mg SC, 2.6% belimumab 200 mg SC).

Laboratory findings

The clinical laboratory profile as well as observations related to vital signs for study BEL112341 was consistent with the IV formulation. There were no new safety concerns.

Reductions in immunoglobins and changes in B cell subsets by belimumab administered SC were similar to those seen in the IV Phase 3 program over the course of 52 weeks. This supports the overall expectation that the long-term safety profile of belimumab 200 mg SC will reflect that of the IV formulation.

Safety in special populations

In study BEL112341, subgroup analyses of AEs by age (<65, ≥ 65 years), gender, race, and body weight were conducted. The AE profile of females was representative of the overall AE profile of the CRD studies since female subjects represented 94.1% of the overall population and the number of male subjects was small. Similarly, <2% of the overall population were ≥ 65 years of age; thus meaningful comparisons in age subgroups or between the treatment groups for the subgroup of subjects ≥ 65 years of age are not possible.

When examined by geographic region revealed similar patterns without imbalances in treatment groups for study BEL112341 and the pooled CRD studies. Also, the incidence of AEs, SAEs, and AESIs was similar in subjects with baseline positive anti-dsDNA and low C3/C4 (anti-dsDNA ≥ 30 IU/mL and at least one C3/C4 low) and NOT with anti-dsDNA ≥ 30 IU/mL and at least one C3/C4 low and with the overall population.

Incidences of AEs and SAEs were generally similar across weight quartiles.

A total of 11 pregnancies were reported during the double-blind phase of the study. Three pregnancies were in subjects receiving placebo: 1 resulted in an induced abortion, 1 was lost to follow-up, and 1 was ongoing at the time of reporting. Eight pregnancies were in subjects receiving belimumab: 4 resulted in a normal live birth with no apparent congenital anomaly, 2 resulted in a spontaneous abortion, 1 resulted in an induced abortion, and 1 was ongoing at the time of reporting.

Safety related to drug-drug interactions and other interactions

The current application did not reveal new safety concerns related to drug-drug interactions and other interactions.

Discontinuation due to adverse events

In study BEL112341, the overall incidence of AEs leading to discontinuation of study agent was 8.9% for the placebo group and 7.2% for the belimumab 200 mg SC group. The most common SOC for AEs leading to discontinuation was infections and infestations (2.5%) for the placebo group and renal and urinary disorders (1.4%) for the belimumab group.

Two subjects treated with belimumab SC discontinued due to mild to moderate injection site-related AEs.

One subject in the belimumab group was discontinued due to swelling face, lip swelling, and anaphylactic reaction (all moderate, possibly related); the subject was not premedicated prior to injection and was treated for the event with depo-medrol 80 mg and celestone soluspan 30 mg.

Overall, the incidence of AEs resulting in study agent discontinuation reported for belimumab 200 mg SC (7.2%) was similar to that for the belimumab group in the pooled IV studies (6.0%).

The overall incidence of AEs leading to discontinuation of study agent during the open-label phase of study BEL112341 was 2.4% for placebo to belimumab 200 mg SC and 2.6% belimumab 200 mg SC). One subject in the placebo to belimumab group discontinued due to local injection site-related AEs. Subject discontinued due to injection site urticaria (mild, definitely related) that occurred 15 days after receiving the first dose of belimumab. One subject in the belimumab 200 mg SC group was discontinued due to SAEs of eyelid edema, lip swelling, rash pruritic, and urticaria (severe, definitely related) that occurred 382 days after receiving the first dose of belimumab and 2 days after the last dose during the open-label phase.

Post marketing experience

Based on sales data, cumulative post marketing exposure up to 08 March 2016 is estimated to be 37,081 patient years. Review of post marketing safety data is conducted on an ongoing basis in order to identify new safety signals which may arise from clinical trial and/or post-marketing reports.

2.6.1. Discussion on clinical safety

A new formulation of belimumab has been developed which enables SC administration utilizing either a prefilled syringe or an autoinjector. The proposed formulation is a 200 mg/mL solution for injection for single 1 mL injection once weekly into either the thigh or the abdomen.

The primary safety population for the belimumab SC formulation was comprised of the subjects from the 52-week pivotal Phase 3 study BEL112341. This pivotal Phase 3 study (fixed dose 200 mg weekly)

targeted a similar average belimumab exposure as the 10 mg/kg IV dose which is marketed and a SLE population consistent with the population studied in the Phase 3 IV trials. Accordingly, the same potential and identified risks, as well as AEs of special interest (AESI) that apply to the IV product were also prospectively-defined AESI for the SC development program.

The primary safety population from the supporting IV program was comprised of subjects from the Phase 2 study LBSL02 and the 2 Phase 3 studies C1056 and C1057. A total of 2969 subjects were included in the ITT population for these CRD studies including 836 subjects in SC study BEL112341 and 2133 subjects in the 3 IV studies. Of these subjects, 68% (2014/2969) were treated with belimumab, 556 subjects with belimumab 200 mg SC and 1458 subjects with belimumab IV (1, 4, or 10 mg/kg). Overall, the approach for the evaluation of safety in the context of the previous IV studies is endorsed.

The overall incidence of AEs reporting for both active and placebo tended to be lower in the SC study as compared to the pooled IV studies. It seems feasible that this might partly relate to a different mode of administration of study agent but possibly also to the SC study being conducted when the IV formulation was already approved (the study was initiated November 2011). Also, there were some differences in enrolment by region with a higher proportion of subjects in study BEL112341 randomized from Eastern Europe and fewer from the US/Canada as compared to the pooled IV studies.

In the pivotal study BEL112341, the AE profile of belimumab 200 mg SC plus standard therapy was generally similar to placebo plus standard therapy. Local injection site reactions did occur more frequently in the belimumab 200 mg SC group (6.1%) than the placebo group (2.5%). These were all mild or moderate in severity with no severe or serious local injection events. No differences were observed between the thigh and abdominal injection sites. Two subjects in the belimumab group discontinued due to a local injection site reaction.

The incidence of post-injection systemic reactions was similar between belimumab 200 mg SC and placebo and this is reassuring, given also the fact that no premedication was stipulated by the study protocol.

The MAH is proposing that the product can be administered outside a clinically supervised setting after the first dose, i.e, after the first supervised injection, a patient may self-inject or the patient caregiver may administer Benlysta provided that the healthcare professional determines that this is appropriate. The section 4.2 of the SmPC has been updated accordingly. Based on the provided clinical study data, this is considered acceptable.

In total, 3 deaths occurred in the belimumab 200 mg SC group that were associated with infections whereas the 2 deaths in the placebo group were associated with cardiovascular and hematologic complications, respectively. These infection fatalities were recently discussed in EMEA/H/C/002015/II/0038 and resulted in updates to sections 4.4 and 4.8 of the SmPC, stating that infections can be severe and fatal and in case of acute infection to consider interrupting immunosuppressant therapy including belimumab until the infection is resolved. The MAH also agreed to submit a renewed cumulative review of fatal infection events within the next PSUR. It is considered that there is no need for further SmPC updates at this time.

A comparative review of other AESI of interest (malignant neoplasms, psychiatric events) did not evoke any new concerns. Malignancy incidence rates were low and similar between the belimumab 200 mg SC and placebo groups in Study BEL112341 and the belimumab IV studies. Similar to the previous IV data, the SC study results showed a slight numeric imbalance regarding incidence of events related to suicide/self-injury, however the numbers of cases were limited and no conclusions could be drawn. This issue will be further followed however as additional controlled study data is expected to be forthcoming, e.g. the CSR for BEL115467 (December 2019).

The reductions in immunoglobins and changes in B cell subsets by belimumab administered SC were similar to those seen in the IV Phase 3 program over the course of 52 weeks, supporting the overall expectation that the long-term safety profile of belimumab 200 mg SC will reflect that of the IV formulation.

Results from the 6-month open-label extension did not evoke any new safety concerns.

No belimumab 200 mg SC subject tested positive for ADAs in the double-blind phase of study BEL112341. Three subjects tested positive following belimumab 200 mg SC administration during the open-label phase or at the 8-Week Follow-up visit. All 3 subjects had negative values on subsequent follow-up testing.

As part of the device bridging program, the usability and reliability of the autoinjector device with respect to chronic real-life use by adult subjects with SLE were evaluated in study 200339. An additional aim was to further characterize the change in belimumab trough concentrations when switching from the IV to the SC. The proposed switching interval of 1-4 weeks after the last intravenous dose is agreed.

No medical device incidents or near incidents were identified during any belimumab SC study. No device functional issues were considered to have impacted safety.

In summary, the safety profile of belimumab SC in the Phase 3 study BEL112341 was consistent with that of IV, and no new safety signals were identified. Similarly, the overall safety profile from the LTC trials to date did not evoke any new concerns. Thus, no changes to the safety specification are warranted except that injection related systemic reactions were added to the identified risks (in addition to infusion related systemic reactions). Based on sales data, cumulative post marketing exposure up to 08 March 2016 is estimated to be 37,081 patient years. Review of post marketing safety data is conducted on an ongoing basis, including the recent PSUSA (period covered: 9 March 2015 to 8 March 2016) which concluded that the benefit/risk profile of belimumab continued to be positive.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

In conclusion, the safety profile of belimumab 200 mg SC appears to be consistent with the known safety profile of the IV formulation.

The Benefit-Risk balance is considered positive from a clinical safety point of view.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Infusion or injection related systemic reactions Hypersensitivity reactions Infections
Important potential risks	Progressive multifocal leukoencephalopathy Malignancies Immunogenicity Effects on Immunisations, including Interactions with Live Vaccines Psychiatric events including depression and suicidality
Missing information	Limited data in pregnant and lactating patients Limited data in elderly patients No data 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

Study/activity Type, title and category (1-3)	*Objectives*	*Safety concerns addressed*	*Status (planned, started)*	*Date for submission of interim or final reports (planned or actual)*
HGS1006-C1074: (BEL112234): A Multi-Center, Continuation Trial of Belimumab (HGS1006, LymphoStat-B™), a Fully Human Monoclonal Anti-BLyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE) who Completed the Phase 3 Protocol HGS1006-C1056 or HGS1006-C1057	Continuation trial of SLE subjects who Completed the Phase III Protocol HGS1006-C1056 or HGS1006-C1057; Canada, EU, Russia, Central America, Asia-Pacific	Long-term safety	Ongoing	CSR = 30 October 2017
HGS1006-C1124 (BEL116543/ SABLE): a 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active,	Prospective observational registry in patients treated with or without belimumab	Long-term safety	Ongoing	Yearly Interim reports 28 February 2014 through 2025, Final CSR = 28 February 2026

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)				
HGS1006-C1101 (BEL114256): Belimumab (BENLYSTA™) Pregnancy Registry protocol	Prospective cohort study. Primary objectives are to evaluate pregnancy and infant outcomes following Benlysta™ exposure and health status of live born infants at 1 year	Safety in pregnancy	Ongoing	Interim report 30 April 2019, Final CSR = 30 April 2022
HGS1006-C1112 (BEL115471): A Phase 3/4, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) in Adult Subjects of Black Race with Systemic Lupus Erythematosus (SLE)	To evaluate the effects of belimumab on the black race because black subjects with higher disease activity (SELENA SLEDAI scores of at least 10) appeared to derive greater benefit with belimumab treatment.	Safety in subjects of black race	Ongoing	CSR = 28 February 2019
HGS1006-C1113 (BEL115467/ BASE): A Randomized, Placebo-Controlled, Study to Assess Adverse Events of Special Interest in Patients with Active, Autoantibody-positive Systemic Lupus Erythematosus	To evaluate the incidence of mortality, selected psychiatric events/suicidality events, serious infusion and hypersensitivity reactions, and where there is a theoretical basis for increased risk with an immunomodulatory treatment (ie, serious/opportunistic	Events of special interest: mortality, selected psychiatric events/suicidality, serious infusion and hypersensitivity reactions, serious/opportunistic infections, and malignancy.	Ongoing	a) 31 December 2016 b) 31 December 2020 c) 31 December 2021 d) 31 December 2022 e) 31

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	infections, malignancy). Also to evaluate steroid reduction at Weeks 40-52. 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			December 2023 CSR for 1yr exposure report = 31 December 2019
HGS1006-C1121 (BEL114054): A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Belimumab plus Standard of Care versus Placebo plus Standard of Care in Adult Subjects with Active Lupus Nephritis	To Evaluate the Efficacy and Safety of Belimumab plus Standard of Care versus Placebo plus Standard of Care in Adult Subjects with Active Lupus Nephritis	Safety in subjects with lupus nephritis	Ongoing	CSR = July 2020
BEL116559: Pooled analysis of elderly patients	Pooled analyses of elderly patients (aged ≥ 65 years) who participated in select belimumab	Safety in elderly subjects	Ongoing	Report 1:Sept 2013 Report 2: July 2016

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	clinical trials.			Report 3: July 2017 Report 4: Dec 2019 Report 5: Feb 2026
BEL116027: A Phase IV, Open-label, Non-randomized, 52-Week Study to Evaluate Treatment Holidays and Rebound Phenomenon After Treatment With Belimumab 10 mg/kg in Systemic Lupus Erythematosus Subjects	To assess the effect of a 24-week withdrawal followed by a 28-week reintroduction of belimumab 10 mg/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 treatment.	Assess the safety of discontinuation and re-introduction of belimumab	Ongoing	CSR = March 2019

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity and Infusion Reactions	**IV SmPC** Posology and method of administration statement on infusion reactions is included in Section 4.2 of the IV SmPC. Benlysta™ treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. Benlysta™ infusions should be administered by a qualified healthcare professional trained to give infusion therapy. Administration of Benlysta™ may result in severe or life-	Distribution of a DHPC to HCPs to inform of the risk of serious hypersensitivity and infusion reactions, and to inform them that some have been observed to have a delayed onset.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	threatening hypersensitivity reactions and infusion reactions. Patients have been reported to develop symptoms of acute hypersensitivity several hours after the infusion has been administered. Recurrence of clinically significant reactions after initial appropriate treatment of symptoms has also been observed. Therefore, Benlysta™ should be administered in an environment where resources for managing such reactions are immediately available. Patients should remain under clinical supervision for a prolonged period of time (for several hours), following at least the first 2 infusions, taking into account the possibility of a late onset reaction. Patients treated with Benlysta™ should be made aware of the potential risk of severe or life-threatening hypersensitivity and the potential for delayed onset or recurrence of symptoms. The package leaflet should be provided to the patient each time Benlysta™ is administered (see section 4.4)." "Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of Benlysta™." "The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction." Warning and precaution statements on infusion reactions are included in Section 4.4 of the IV SmPC. "Infusion reactions and hypersensitivity Administration of Benlysta™ may result in hypersensitivity reactions and infusion reactions which can be severe and fatal. In the event of a severe reaction, Benlysta™ administration must be interrupted and appropriate medical therapy administered	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	(see section 4.2). The risk of hypersensitivity reactions is greatest with the first two infusions; however the risk should be considered for every infusion administered. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. Patients should be advised that hypersensitivity reactions are possible, on the day of, or several days after infusion, and be informed of potential signs and symptoms and the possibility of recurrence. Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of Benlysta™. There is insufficient knowledge to determine whether premedication could diminish the frequency or severity of infusion reactions. In clinical studies, serious infusion and hypersensitivity reactions affected approximately 0.9% of patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Infusion reactions occurred more frequently during the first two infusions and tended to decrease with subsequent infusions (see section 4.8). Patients have been reported to develop symptoms of acute hypersensitivity several hours after the infusion has been administered. Recurrence of clinically significant reactions after initial appropriate treatment of symptoms has also been observed (see section 4.2 and 4.8). Therefore, Benlysta™ should be administered in an environment where resources for managing such reactions are immediately available. Patients should remain under clinical supervision for a prolonged period of time (for several hours), following at least the first 2 infusions, taking into account the possibility of a late onset reaction. Patients should be advised that hypersensitivity	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reactions are possible on the day of, or several days after infusion, and be informed of potential signs and symptoms and the possibility of recurrence. Patients should be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet should be provided to the patient each time Benlysta™ is administered (see section 4.2). Statements on infusion reactions are included in Section 4.8 "Undesirable Effects" of the SmPC. The safety of belimumab in patients with SLE has been evaluated in 3 placebo-controlled studies and 1 placebo-controlled subcutaneous study. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequency given is the highest seen with either formulation Infusion or injection-related systemic reactions* were reported as common (≥1/100 to <1/10). Anaphylactic, angioedemareactions were reported as uncommon (≥1/1,000 to <1/100) *'Hypersensitivity reactions' covers a group of terms, including anaphylaxis, and can manifest as a range of symptoms including hypotension, angioedema, urticaria or other rash, pruritus, and dyspnoea. 'Infusion or injection-related systemic reactions' covers a group of terms and can manifest as a range of symptoms including bradycardia, myalgia, headache, rash, urticaria, pyrexia, hypotension, hypertension, dizziness, and arthralgia. Due to overlap in signs and symptoms, it is not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases. *Description of selected adverse reactions* Data presented below include pooled rates from the	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	intravenous clinical trials (10 mg/kg IV dose only) and the subcutaneous clinical trial. Infusion or injection related systemic reactions and hypersensitivity: Infusion or injection-related systemic reactions and hypersensitivity were generally observed on the day of administration, but acute hypersensitivity reactions may also occur several days after dosing. Patients with a history of multiple drug allergies or significant hypersensitivity reactions may be at increased risk. The incidence of infusion reactions and hypersensitivity reactions occurring within 3 days of an infusion was 12% in the group receiving Benlysta™ and 10% in the group receiving placebo, with 1.2% and 0.3%, respectively, requiring permanent treatment discontinuation. **SC SmPC** Posology and method of administration statement on infusion reactions is included in Section 4.2 of the SC SmPC. It is recommended that the first subcutaneous injection of Benlysta™ should be under the supervision of a healthcare professional in a setting that is sufficiently qualified to manage hypersensitivity reactions, if necessary. The healthcare professional must provide proper training in subcutaneous technique and education about signs and symptoms of hypersensitivity reactions. A patient may self-inject or the patient's caregiver may administer Benlysta™ after the healthcare professional determines that it is appropriate. Warning and precaution statements on hypersensitivity reactions are included in Section 4.4 of the SC SmPC. Administration of subcutaneous or intravenous Benlysta™ may result in hypersensitivity	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reactions which can be severe, and fatal. In the event of a severe reaction, Benlysta™ administration must be interrupted and appropriate medical therapy administered. The risk of hypersensitivity reactions is greatest with the first two doses; however the risk should be considered for every administration. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. Recurrence of clinically significant reactions after initial appropriate treatment of symptoms has also been observed. Patients should be advised that hypersensitivity reactions are possible, on the day of, or several days after administration, and be informed of potential signs and symptoms and the possibility of recurrence. Patients should be instructed to seek immediate medical attention if they experience any of these symptoms. The package leaflet should be provided to the patient. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema. In intravenous clinical studies, serious infusion and hypersensitivity reactions included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnoea. Section 4.8 “Undesirable Effects” of the SC SmPC. The safety of belimumab in patients with SLE has been evaluated in 3 placebo-controlled intravenous studies and 1 placebo-controlled subcutaneous study. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequency given is the highest seen with either formulation. Infusion or injection-related systemic reactions* were	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reported as common (≥1/100 to <1/10). Anaphylactic, angioedema reactions were reported as uncommon (≥1/1,000 to <1/100). *'Hypersensitivity reactions' covers a group of terms, including anaphylaxis, and can manifest as a range of symptoms including hypotension, angioedema, urticaria or other rash, pruritus, and dyspnoea. 'Infusion or injection-related systemic reactions' covers a group of terms and can manifest as a range of symptoms including bradycardia, myalgia, headache, rash, urticaria, pyrexia, hypotension, hypertension, dizziness, and arthralgia. Due to overlap in signs and symptoms, it is not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases. Injection site reactions** were reported as common (≥1/100 to <1/10). ** Applies to subcutaneous formulation only Description of selected adverse reactions: Data presented below are pooled from the intravenous clinical trials ((10 mg/kg IV dose only)) and the subcutaneous clinical trial. Infusion or injection-related systemic reactions and hypersensitivity: Infusion or injection-related systemic reactions and hypersensitivity were generally observed on the day of administration, but acute hypersensitivity reactions may also occur several days after dosing. Patients with a history of multiple drug allergies or significant hypersensitivity reactions may be at increased risk. Clinically significant hypersensitivity reactions associated with Benlysta™ administered subcutaneously and requiring permanent treatment discontinuation were reported in 0.2% of patients. Injection site reactions:	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	In the subcutaneous trial, the frequency of injection site reactions was 6.1% (34/556) and 2.5% (7/280) for patients receiving Benlysta™ and placebo, respectively. These injection site reactions (most commonly pain, erythema, hematoma, pruritus and induration) were mild to moderate in severity. The majority did not necessitate drug discontinuation.	
Infections	**IV SMPC** Warning and precaution statements on risk of infection are included in Section 4.4 of the IV SmPC. "The mechanism of action of Benlysta™ could increase the risk for the development of infections including opportunistic infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant pharmacotherapy, including Benlysta™. Physicians should exercise caution when considering the use of Benlysta™ in patients with a severe or chronic infection or a history of recurrent infection. Patients who develop an infection while undergoing treatment with Benlysta™ should be monitored closely and consideration should be given to stopping immunosuppressant therapy. The risk of using Benlysta™ in patients with active or latent tuberculosis is unknown" Statements on infections are included in Section 4.8 "undesirable effects" of the IV SmPC. The safety of Benlysta™ in patients with SLE has been evaluated in 3 placebo-controlled studies and 1 placebo-controlled subcutaneous study. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequency given is the highest seen with either formulation. Infections reported as very common (≥ 1/10) is bacterial infections, e.g., bronchitis,	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	urinary tract infections. Common (≥1/100 to <1/10) events include, gastroenteritis viral, pharyngitis, nasopharingitis, viral upper respiratory tract infection. Description of selected adverse reactions: Infections: The overall incidence of infections in IV and SC studies was 63% in both groups receiving Benlysta™ or placebo.. Infection occurring in at least 3% of patients receiving belimumab and at least 1% more frequently than patients receiving placebo were viral upper respiratory tract infection, bronchitis and urinary tract infection bacterials. Serious infections occurred in 5% in both groups receiving Benlysta™ or placebo; serious opportunistic infections accounted for 0.4% and 0% of these, respectively. Infections leading to discontinuation of treatment occurred in 0.7% of patients receiving Benlysta™ and 1.5% of patients receiving placebo. **SC SmPC** Warning and precaution statements on risk of infection are included in Section 4.4 of the SC SmPC. The mechanism of action of belimumab could increase the risk for the development of infections, including opportunistic infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant pharmacotherapy, including Benlysta™. Physicians should exercise caution when considering the use of Benlysta™ in patients with severe or chronic infections or a history of recurrent infection. Patients who develop an infection while undergoing treatment with Benlysta™ should be monitored closely and consideration should be given to stopping immunosuppressant therapy until infection is resolved. The risk of using	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Benlysta™ in patients with active or latent tuberculosis is unknown. Section 4.8 “Undesirable Effects” of the SC SmPC. The safety of belimumab in patients with SLE has been evaluated in 3 placebo-controlled intravenous studies and 1 placebo-controlled subcutaneous study. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequency given is the highest seen with either formulation. Infection reported as very common (≥ 1/10) is bacterial infections, e.g, bronchitis and urinary tract infection. Common (≥1/100 to <1/10) events include, gastroenteritis viral, pharyngitis, nasopharingitis, viral upper respiratory tract infection. Description of selected adverse reactions: Data presented below are pooled from the intravenous clinical trials (10 mg/kg IV dose only) and the subcutaneous clinical trial The overall incidence of infections was 63% in both groups receiving Benlysta™ or placebo. Infection occurring in at least 3% of patients receiving Benlysta™ and at least 1% more frequently than patients receiving placebo were viral upper respiratory tract infection, bronchits, and urinary tract infection bacterial. Serious infections occurred in 5% in both groups receiving Benlysta™ or placebo; serious opportunistic infections accounted for 0.4% and 0% of these, respectfully. Infections leading to discontinuation of treatment occurred in 0.7% of patients receiving Benlysta™ and 1.5% of patients receiving placebo.	
Progressive Multifocal Leukoencephalopathy	**IV and SC SmPCs** Warning and precaution statements on risk of infection are included in Section 4.4 of the SmPC. EMA SmPC text agreed:	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	"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 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."	
Malignancies	**IV and SC SmPC** A Warning and precaution statement on malignancies and lymphoproliferative disorders is included in Section 4.4 of the IV and SC SmPCs. Immunomodulatory medicinal products, including Benlysta™, may increase the risk of malignancy. Caution should be exercised when considering Benlysta™ therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. Patients with malignant neoplasm within the last 5 years have not been studied, with the exception of those with basal or squamous cell cancers of the skin, or cancer of the uterine cervix, that has been fully excised or adequately treated.	None
Immunogenicity	Section 5.1 of the IV SmPC describes the immunogenic potential for belimumab. "Assays sensitivity for neutralizing antibodies and non-specific anti-drug antibody (ADA) are limited by the presence of active drug in the collected samples. The true occurrence of neutralizing antibodies and non-specific anti-drug antibody in the study population is therefore not known." In the two Phase 3 studies, 4 out of 563 (0.7%) patients in	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the 10 mg/kg group and 27 out of 559 (4.8%) patients in the 1 mg/kg group tested positive for persistent presence of anti-belimumab antibodies." "Among persistent-positive subjects in the Phase 3 trials, 1/10 (10%) , 2/27 (7%) and 1/4 (25%) subjects in the placebo, 1 mg/kg and 10 mg/kg groups, respectively, experienced infusion reactions on a dosing day; these infusion reactions were all non-serious and mild to moderate in severity. Few patients with ADA reported serious/severe AEs. The rates of infusion reactions among persistent-positive subjects were comparable to the rates for ADA negative patients of 75/552 (14%), 78/523 (15%), and 83/559 (15%) in the placebo, 1 mg/kg and 10 mg/kg groups, respectively." **SC SmPC** Section 5.1 of the SC SmPC. In the SC study where serum samples from more than 550 patients with SLE were tested, no anti-belimumab antibodies were detected during or after treatment with belimumab 200 mg subcutaneously.	
Effect on Immunisations, Including Interactions with Live Vaccines	**IV and SC SmPC** Warning and precaution statements on immunisations are included in Section 4.4 of the SmPCs: Live vaccines should not be given for 30 days before, or concurrently with Benlysta™ as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving Benlysta™. Because of its mechanism of action, belimumab may interfere with the response to immunisations. However, in a small study evaluating the response to a 23-valent pneumococcal vaccine, overall immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving belimumab at the	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	time of vaccination. Limited data suggest that Benlysta™ does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of Benlysta™. In a Benlysta™ IV substudy, a small group of patients who had previously received either tetanus, pneumococcal or influenza vaccinations were found to maintain protective titres after treatment with Benlysta™. There are insufficient data to draw conclusions regarding the ability of subjects receiving belimumab to mount protective responses to vaccines.	
Psychiatric events including depression and suicidality	**IV and SC SmPC** Statements on psychiatric events are included in Section 4.8 "Undesirable Effects" of the SmPC. The safety of belimumab in patients with SLE has been evaluated in 3 placebo-controlled studies and 1 placebo-controlled subcutaneous study. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The frequency given is the highest seen with either formulation. Depression, is reported as common (≥1/100 to <1/10). Description of selected adverse reactions: Data presented below are pooled from the intravenous clinical trials (10 mg/kg IV dose only) and the subcutaneous clinical trial. "Psychiatric disorders: The incidence of depression reported as an adverse event was 3% in both groups receiving Benlysta™ or placebo.	None

No new additional risk minimisation measures are proposed by the Applicant as a result of this application.

The risk minimisation measures for subcutaneous administration are based on routine risk minimisation activities which in principle are deemed adequate.

Conclusion

The CHMP and PRAC considered that the risk management plan version 24 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. 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

This application refers to a new pharmaceutical form (SC) to be administered once weekly. The recommended dosage is 200 mg once weekly given as a SC injection in the abdomen or thigh.

The proposed indication for SC belimumab is the same as that already approved for IV use of belimumab in the EU:

Belimumab is indicated as add-on therapy in adult patients 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

3.1.2. Available therapies and unmet medical need

Patients with high disease activity despite corticosteroids and standard immunosuppressants are in need of additional treatment options. There have been no additional medicinal products approved for SLE since the approval of the IV formulation of belimumab in 2011.

The proposed SC formulation would constitute a more flexible method of receiving belimumab for the targeted population.

3.1.3. Main clinical studies

The MAH conducted a single pivotal Phase 3 randomized double-blind placebo-controlled 52 week trial (BEL 112341) to support the SC formulation. The aim of this study was to evaluate the efficacy and safety of belimumab administered SC in adult subjects with active SLE. For the most part, the critical design elements of this SC study were the same as those utilized for the previous pivotal Phase 3 IV program.

Subjects were randomized to belimumab or placebo (2:1 ratio) 200 mg belimumab weekly or placebo SC weekly. Belimumab was administered SC on Day 0 and weekly thereafter to Week 51.

A few adaptations were made compared to the clinical program of the IV formulation, including the use of raised entry criteria for the SELENA SLEDAI score at screening from ≥ 6 to≥ 8. This change was made based on the results from the IV studies which showed that patients with higher disease activity, as reflected by a higher SELENA SLEDAI score, were more likely to respond to belimumab. Eligible subjects had also either an unequivocally positive ANA and/or positive antidouble anti-dsDNA) serum antibody test result and were on a stable SLE treatment regimen.

The primary efficacy endpoint was the SLE responder index (SRI) response rate at Week 52 identical to the pivotal IV studies. 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 Physician's Global Assessment (PGA), AND no new British Isles Lupus Assessment Group (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).

836 subjects (280 in the placebo group and 556 in the belimumab 200 mg SC group) in the ITT population were enrolled across 177 sites.

The applicant also performed a phase 2 study to assess the auto-injector device for self-administration of belimumab outside a clinically supervised setting after the first dose. This study demonstrated the feasibly of self-administration, which is reflected in the SmPC.

3.2. Favourable effects

In BEL112341, the SRI response at Week 52 was positive and statistically significant (48.4% placebo, 61.4% belimumab, odds ratio [OR] 1.68; 95% CI: 1.25. 2.25; p=0.0006). The individual components of the SRI in BEL112341 all reached statistical significance for belimumab SC vs. placebo (all p<0.05).

The response was numerically superior for belimumab SC starting at Week 8. Statistical significance was reached by Week 16 and was maintained through Week 52. Prespecified sensitivity analyses of the primary endpoint were consistent with the primary analyses.

Time to first severe flare, as measured by the modified SLE flare index (SFI), was a major secondary efficacy endpoint. The belimumab 200 mg SC group had a 49% reduced risk of severe flare compared to placebo (hazard ratio [HR] 0.51; 95% CI: 0.35, 0.74; p=0.0004).

The second major secondary endpoint in BEL112341 was the percentage of subjects whose average prednisone dose was reduced by ≥ 25% from baseline to ≤ 7.5mg/day during the last 12 weeks of the study in the subgroup of subjects who were receiving >7.5mg/day of prednisone at baseline (60.2% of subjects). Subjects receiving belimumab were numerically more often able to achieve prednisone dose reduction than placebo subjects (18.2% vs. 11.9%; OR 1.65; 95% CI: 0.95, 2.84; p=0.0732).

While the SC formulation represents a fixed dosing regimen (in contrast to the IV formulation which is dosed at mg/kg), higher body weight did not result in lower SRI response to belimumab SC.

SRI subgroup analysis was performed using 3 definitions of high disease activity: a SELENA SLEDAI score of ≥ 10, low C3 and/or low C4, and the combination of anti-dsDNA positivity and low complement. Analysis of the major secondary endpoints was also performed for those subjects with both anti-dsDNA positivity and low complement.

A more robust effect of belimumab treatment was observed in subjects with higher levels of disease activity. Subjects with low complement and positive anti-dsDNA demonstrated a treatment difference for belimumab relative to placebo of 17.41% more responders (odds ratio 2.23; 95% CI: 1.36, 3.64; p=0.0014) (as compared to a delta of 9.64 for the not low complement/anti-dsDNA subgroup and 12.98 for the overall population). This subgroup also showed a more pronounced effect on prevention of severe flare with 62% reduced risk of severe flare compared to placebo (HR 0.38; p <0.0001) than the overall population (whereas the 'not low complement/anti-dsDNA subgroup' was not statistically significant). The other major secondary endpoint relating to prednisone reduction did not reach statistical significance ((20.7% vs. 11.4%; p=0.0844).

In BEL112341, entry requirements for SELENA SLEDAI were slightly higher compared to the IV study program. However, a post-hoc analysis was conducted of this same subgroup (baseline SELENA SLEDAI score ≥ 8) in the IV Phase 3 trials showed results consistent with the SC trial.

Pharmacokinetic data has shown that the median concentrations at steady state after SC administration of 200 mg weekly was close to steady state Cav after administration of 10 mg/kg every 4 weeks in the IV program.

3.3. Uncertainties and limitations about favourable effects

Overall, the results from study BEL112341 are quite consistent with the efficacy demonstrated in the IV Phase 3 registration program (studies C1056 and C1057).

Evaluation of the long-term efficacy of belimumab continues in one ongoing IV extension studies (HGS1006-C1074) for subjects who satisfactorily completed the Phase 3 controlled repeat-dose IV studies. There are several ongoing post-marketing studies of belimumab in SLE populations not previously evaluated. In particular, studies are on-going in pregnancy, in the elderly population were clinical data are lacking. In addition, there is a lack of data in SLE patients with severe active lupus nephritis or severe active CNS lupus, this is being investigated. Finally the lack of data on effect of stopping treatment and risk of rebound phenomenon has not yet been addressed. These studies have

been agreed as part of the IV formulation and are ongoing. However they are also relevant to this new formulation.

3.4. Unfavourable effects

In the pivotal study BEL112341, the AE profile of belimumab 200 mg SC plus standard therapy was generally similar to placebo plus standard therapy. Local injection site reactions did occur more frequently in the belimumab 200 mg SC group (6.1%) than the placebo group (2.5%). These were all mild or moderate in severity with no severe or serious local injection events. No differences were observed between the thigh and abdominal injection sites.

Mild to moderate local injection site reactions occurred more frequently in the belimumab 200 mg SC group (6.1%) than the placebo group (2.5%) and 2 subjects in the belimumab group discontinued due to a local injection site reaction.

The incidence of post-injection systemic reactions was similar between belimumab 200 mg SC and placebo.

In total, 3 deaths occurred in the belimumab 200 mg SC group that were associated with infections whereas the 2 deaths in the placebo group were associated with cardiovascular and hematologic complications, respectively. Similarly to the IV formulation, infections can be severe and fatal and in case of acute infection to consider interrupting immunosuppressant therapy including belimumab until the infection is resolved. No new safety concern was raised with this formulation. Additionally a comparative review of other AESI of interest (malignant neoplasms, psychiatric events) did not raise any new concerns.

In summary, the safety profile of belimumab SC in the Phase 3 study BEL112341 was consistent with that of the IV formulation.

3.5. Uncertainties and limitations about unfavourable effects

The Company is proposing that the product be self-administered outside a clinically supervised setting after the first dose. This is acceptable and this will be monitored through pharmacovigilance in the post marketing setting in PSURs.

Following the approval of the IV formulation, the long-term safety of belimumab is still being investigated in several ongoing postmarketing studies and a 5-year prospective observational registry (BEL116543/SABLE) is in place.

3.6. Effects Table

Table 27: Effects table for Benlysta as add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) despite standard therapy (13 February 2015)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects*						

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
SRI response rate at Week 52	SELENA SLEDAI ≥4 point reduction and no worsening as measured by PGA and BILAG	%	64.6	47.2	17.4% difference vs. placebo OR (95% CI) vs. placebo: 2.23 (1.36, 3.64) p=0.0014	Pivotal study BEL112341
Time to first severe flare over 52 wks	Time to first severe flare, but excluding flares triggered only by increase in SELENA SLEDAI score to >12	%	14.1	31.5	HR (95% CI): 0.38 (0.24, 0.61) p<0.0001	
% subjects with dose of prednisone reduced by ≥25% from baseline to ≤7.5 mg/ day during Wks 40-52	Includes only the subgroup of subjects with baseline prednisone >7.5 mg/day	%	20.7	11.4	OR (95% CI) vs. placebo: 2.08 (0.91, 4.77) p=0.0844	
Unfavourable Effects**						
Deaths		n (%)	3 (0.5)	2 (0.7)	deaths in belimumab group were due to infection and deaths in placebo group were cardiac arrest, thrombocytopenia	Pivotal study BEL112341
Serious infections		n (%)	23 (4.1)	15 (5.4)	Serious infections of special interest (AESI): 8 (1.4%) vs. 3 (1.1%) for placebo	
Malignancy	including NMSC	n (%)	2 (0.4)	1 (0.4)	Follow-up time too short to draw conclusions	
Depression/ Suicidality/ Self-injury		n (%)	17 (3.1)	10 (3.6)	Numerically more suicide/self-injury in belimumab group 2 (0.4%) vs. 0 for placebo.	
Post-injection systemic reactions		n (%)	38 (6.8)	25 (8.6)	Question regarding the definitions/ search strategy compared to the IV program. No ADAs detected.	
Local injection reactions		n (%)	34 (6.1)	7 (2.5)	No correlation to injection site (abdomen or thigh). No ADAs detected	

Abbreviations: ADA: anti-drug antibodies; C3/C4: complement components.
Notes: *Primary and Major Secondary Endpoint results reflect the subgroup of subjects with both anti-dsDNA ≥30 IU/mL and low C3 and/or low C4 (belimumab: n=248; placebo: n=108).
** Data reflect the Safety population of study BEL112341 (belimumab: n=556; placebo: n=280).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The results from the belimumab SC Phase 3 trial, BEL112341 using belimumab 200 mg SC once weekly as an add-on treatment to standard therapy in adult patients with active autoantibody-positive SLE are consistent with the efficacy demonstrated in the previous Phase 3 registration program for the IV Benlysta formulation. Similar to the IV studies, a more robust effect of belimumab treatment was observed in subjects with higher levels of disease activity. This support the use of belimumab SC for the same indication as currently approved for the IV formulation, i.e. as add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity (e.g positive anti-dsDNA and low complement) despite standard therapy. Patients with high disease activity despite standard care are also those with the greatest unmet medical need.

A subcutaneous (SC) formulation of belimumab for weekly, fixed-dose administration constitute a more flexible method of receiving belimumab for these patients, thereby avoiding infusion therapy. Additionally, self-administration by patients or caregivers (after the first supervised dose) would also be advantageous.

The local injection site reactions observed are acceptable and the incidence of post-injection systemic reactions was similar between belimumab 200 mg SC and placebo.

The safety profile of belimumab is based on the SC Phase 3 trial BEL112341, supported by and consistent with, a large safety database from the IV formulation. Effects on B cell subsets and immunoglobin levels by belimumab administered SC reflected those observed in the IV Phase 3 program. Thus, overall, a similar long-term safety profile is anticipated.

3.7.2. Balance of benefits and risks

The data provided in this application are considered acceptable to support the approval of belimumab SC formulation as an add-on therapy on top of standard of care for patients with autoantibody positive SLE with high disease activity.

A subcutaneous (SC) formulation of belimumab constitute a more flexible method of administration for the patients, thereby avoiding infusion therapy. Additionally, self-administration by patients or caregivers (after the first supervised dose) would also be advantageous in the daily practice.

3.8. Conclusions

The overall B/R of Benlysta is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Benlysta 200mg, solution for injection in syringes and syringes in prefilled pen is favourable in the following indication:

Benlysta is indicated as add-on therapy in adult patients 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 CHMP therefore recommends the extension(s) of the marketing authorisation for Benlysta subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

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.

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.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
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.	31 December 2019
The MAH shall also 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).	28 February 2026

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation concerning the following change(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC as a consequence of the data package submitted to support the new proposed solution for injection subcutaneous presentations. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0 and to introduce some editorial changes.