DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY SAFETY ASSESSMENT OF EXTRACTABLES
AND LEACHABLES FOR BENLYSTA® (BELIMUMAB)

Application number: BLA 761043
Supporting document/s: SDN#1
Applicant's letter date: September 22, 2016
CDER stamp date: September 22, 2016
Product: BENLYSTA® (Belimumab)
Indication: Systemic lupus erythematosus
Applicant: Human Genome Sciences (GSK)
Review Division: Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer: Brett Jones, PhD
Supervisor (Acting): Andrew Goodwin, PhD
Division Director: Badrul Chowdhury, MD, PhD
Project Manager: Jessica Lee

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1 Executive Summary

1.1 Introduction
The Sponsor submitted the present Biologics License Application (BLA) 761043 on September 22, 2016 to support the marketing approval of BENLYSTA subcutaneous injection.

BENLYSTA® is currently approved for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The recommended dosage regimen is 10 mg/kg intravenously (IV) at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

For the current submission, the Sponsor has proposed BENLYSTA (200 mg) be administered subcutaneously (SC) once weekly in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The application includes a 200 mg (in 1 mL) single-dose autoinjector and a 200 mg (in 1 mL) single-dose prefilled syringe for self-administration. This review is a nonclinical safety evaluation of potential leachables for the BENLYSTA subcutaneous drug product.

The overall nonclinical pharmacology and toxicology evaluation, as well as labeling recommendations, was provided in a separate review dated May 9, 2017.

1.2 Brief Discussion of Nonclinical Findings
There are no nonclinical safety concerns based on the results from the leachables studies.

2 Drug Information

2.1 Drug
CAS Registry Number
356547-88-1

Tradename
BENLYSTA®

Generic Name
Belimumab

Molecular Formula/Molecular Weight
147 KDaltons
Structure or Biochemical Description
Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

Pharmacologic Class
BENLYSTA® (belimumab) is a human IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLYS, also referred to as BAFF and TNFSF13B)

2.2 Relevant INDs, NDAs, BLAs and DMFs
BLA 125370 (Belimumab, GSK)

2.3 Drug Formulation
Each prefilled syringe of belimumab drug product is intended to deliver 200 mg of sterile liquid belimumab. The composition per dose is 200 mg/mL belimumab in a formulation containing histidine, sodium chloride, arginine hydrochloride and polysorbate 80 at a pH of 6.0 (see table below).

(Excerpt from Sponsor’s submission)
Table 1. Composition of Belimumab Drug Product per Dose

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity (mg/mL)</th>
<th>Function</th>
<th>Quality Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belimumab</td>
<td>200</td>
<td>Active substance</td>
<td>In house Specification</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>6.7</td>
<td></td>
<td>USP, Ph. Eur., JP</td>
</tr>
<tr>
<td>L-Arginine Hydrochloride</td>
<td>5.3</td>
<td></td>
<td>USP, Ph. Eur., JP</td>
</tr>
<tr>
<td>L-Histidine Monohydrochloride</td>
<td>1.2</td>
<td></td>
<td>Ph. Eur, JP</td>
</tr>
<tr>
<td>L-Histidine</td>
<td>0.65</td>
<td></td>
<td>USP, Ph. Eur., JP</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>0.1</td>
<td></td>
<td>USP-NF, Ph. Eur., JP</td>
</tr>
</tbody>
</table>

2.4 Comments on Novel Excipients
Benlysta is currently marketed as 120 mg or 400 mg lyophilized powder for concentrate for solution for intravenous infusion. After reconstitution, the solution contains 80 mg
belimumab per mL. The approved formulation contains citric acid, sodium citrate, sucrose (80 mg/mL), and polysorbate 80.

The composition of the proposed Benlysta drug product for subcutaneous use is provided above. There are no safety concerns with the excipients in the proposed Benlysta subcutaneous formulation.

2.5 Comments on Extractables and Leachables Studies

This review is a nonclinical safety evaluation of potential leachables for the BENLYSTA subcutaneous drug product. Described in this section are the studies and results; the nonclinical safety evaluation is included in the Integrated Summary and Safety Evaluation section.

Belimumab injection for subcutaneous use (200 mg/1.0 mL) is supplied as a single-use, sterile liquid drug product in two formats. The formats include a prefilled syringe assembled with additional functional components to create an autoinjector, referred to as belimumab drug product (DP) in autoinjector, 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 subcutaneous use. The belimumab DP container closure consists of a 1 mL long, Type I glass syringe with staked needle (27G, ½ inch), rubber plunger stopper, and a rigid needle shield.

(Excerpt from Sponsor's submission)

Figure 1. Appearance of the Belimumab drug product prefilled syringe container closure

According to the Sponsor’s report, the study and evaluation of leachables in belimumab subcutaneous drug product followed a risk-based, three-step approach (e.g., risk assessment process, extractable studies, leachable method development). The risk
assessment covered not only the storage and use of the drug product but also the manufacturing process. The design of the extractables and leachables assessments (i.e., threshold-based approach) was similar to the risk-based approach for the safety assessment of leachables as described by the Product Quality Institute (PQRI) Leachables and Extractables Working Group – Guideline for safety threshold and best practices for extractables and leachables in orally inhaled and nasal drug products. The Sponsor set the threshold for detection, identification, and quantification of leachables within the experimental studies at $\text{mcg/day}$.

**Extractables Studies**
The Sponsor evaluated the failure modes associated with the interaction between the container closure system and the drug product (see table below). The materials of the container closure system were subjected to a range of both extractable and leachable studies.

(Excerpt from Sponsor’s submission)

**Table 2. Failure modes associated with the long term storage and use of the drug product, and summary of degree of risk**

<table>
<thead>
<tr>
<th>Type of unit operation</th>
<th>Failure Mode</th>
<th>Degree of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long term storage and use of the drug product</td>
<td>Through contact with the drug product solution, leach from the walls of the glass barrel</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Through contact with the drug product solution, leaches from the walls of the glass barrel</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Through contact with the drug product solution, leach from the syringe needle</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Through contact with the drug product solution, components leach from the stopper</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>Through long term storage in close proximity to the drug product solution, volatile components leach from the needle shield into the drug product solution</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Through long term storage in close proximity to the drug product solution, components leach from the materials used in the assembled autoinjector device, through the glass syringe barrel and/or stopper, into the drug product solution</td>
<td>Low</td>
</tr>
</tbody>
</table>

Several studies were conducted on syringe stoppers and syringe needle shields to determine any volatile, semi-volatile, and non-volatile extractables. Volatile extractables in stoppers and needle shields were determined by carrying out HS/GC-MS analysis on dry headspace samples, and on extracts from model solvent systems designed to be representative of the final drug formulation. Semi-volatile extractables in stoppers and needle shields were determined by carrying out GC-MS analysis on extracts from the same model solvent systems discussed above. Non-volatile extractables in stoppers were determined by carrying out ultra performance liquid chromatography (UPLC) coupled with high resolution accurate mass spectrometry on extracts from the same model solvent systems. Several volatile, semi-volatile, and non-volatile extractables were
observed at levels at or above the reporting threshold (see table below). The Sponsor stated that none were significantly above this level. No further details were provided.

(Excerpt from Sponsor’s submission)

<table>
<thead>
<tr>
<th>Type of Extractable</th>
<th>Extractable</th>
<th>CAS Number</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volatile</td>
<td></td>
<td></td>
<td>Stoppers</td>
</tr>
<tr>
<td>Semi-Volatile</td>
<td></td>
<td></td>
<td>Stoppers</td>
</tr>
<tr>
<td>Semi-Volatile</td>
<td></td>
<td></td>
<td>Needle Shields</td>
</tr>
<tr>
<td>Semi-Volatile &amp; Non-Volatile</td>
<td></td>
<td></td>
<td>Stoppers &amp; Needle Shields</td>
</tr>
<tr>
<td>Semi-Volatile &amp; Non-Volatile</td>
<td></td>
<td></td>
<td>Stoppers &amp; Needle Shields</td>
</tr>
<tr>
<td>Non-Volatile</td>
<td></td>
<td></td>
<td>Stoppers</td>
</tr>
<tr>
<td>Non-Volatile</td>
<td></td>
<td></td>
<td>Stoppers</td>
</tr>
</tbody>
</table>

An extractables study was also conducted to determine if any levels of metal extractables were present in the syringe stoppers, the syringe needle shields, and the 1 mL syringe barrels and needles. The Sponsor stated that the metal extractables study was conducted as a limit test with a range of different action thresholds, based on % of those listed in the

The results of the limit test indicated that there were no metal extractables above these threshold limits. No further details were provided.

The syringe barrels and needles were also subjected to a specific study for levels of . The Sponsor stated that the study was also conducted as a limit test; however the action threshold was based on % of an internal GSK specification. The results of the limit test indicated that there were no extractable levels. No further details were provided.

The Sponsor’s report stated that was added to the container closure system to maintain its correct operation. An extractable study was not conducted with . The Sponsor stated that a leachables study was conducted to monitor the levels of that are transferred from the surfaces of the components of the container closure system into the drug product.
**Leachables Assessment**
The leachable studies evaluated compounds that had leached from the container closure system into the drug product. The extractable studies described above guided the leachable evaluation. According to the Sponsor's report, four leachable methods were developed to study leachables. The methods used in the leachable studies were:

1. Analysis of volatile leachables in Belimumab SC DP (GSK1550188) by Headspace GC-FID
2. Analysis of semi-volatile leachables in Belimumab SC DP (GSK1550188) by GC-FID
3. Analysis of leachable [mask] in Belimumab SC DP (GSK1550188) by graphite furnace atomic absorption spectroscopy (GF-AAS)
4. Analysis of [mask] in Belimumab SC DP (GSK1550188) by ICP-MS

The validated methods were used to monitor leachables in stored Belimumab SC DP (3 batches) under long-term, accelerated, and stressed storage conditions. Samples stored under long-term storage conditions were kept at 2-8°C/ambient humidity, accelerated storage conditions at 25°C/60% RH, and stressed samples under storage conditions of 40°C/75% RH. For the three batches of Belimumab SC DP, the testing for potential leachables is planned after storage of up to 60 months (i.e., 60 months representing the proposed shelf-life). To date, test points up to 24 months of storage are reported (see tables below). All samples were stored in a horizontal orientation, as this maximized contact between the stopper and the liquid drug product.

(Excerpt from Sponsor's submission)

**Table 4. Summary of Benlysta SC DP leachable studies**

<table>
<thead>
<tr>
<th>Storage Test Type</th>
<th>Storage Condition</th>
<th>Storage Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Init 1 2 3 6 9 12 18 24 30 42 48 60</td>
<td></td>
</tr>
<tr>
<td>Long Term</td>
<td>2-8°C/ambient RH Horizontal</td>
<td>X X X X X X X X X X X X</td>
</tr>
<tr>
<td>Accelerated</td>
<td>25°C/60% RH Horizontal</td>
<td>X X X X - - - - - - -</td>
</tr>
<tr>
<td>Stressed</td>
<td>40°C/75% RH Horizontal</td>
<td>X X X X - - - - - - -</td>
</tr>
</tbody>
</table>

**Legend:**
- Init = Initial time point
- X = Scheduled testing comprising [mask]
- [mask] = No testing scheduled at this time point/condition

Reference ID: 4113084
(Excerpt from Sponsor’s submission)

Table 5. Summary of Benlysta SC DP volatile and semi-volatile leachable studies

<table>
<thead>
<tr>
<th>Storage Test Type</th>
<th>Storage Condition</th>
<th>Storage Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Init 3 4 6 12 18 24 36 48 60</td>
</tr>
<tr>
<td>Long Term</td>
<td>2-8°C/ambiente RH Horizontal</td>
<td>(X) X X X X X X X</td>
</tr>
<tr>
<td>Accelerated</td>
<td>25°C/60% RH Horizontal</td>
<td>(X) (X) X - - - - -</td>
</tr>
<tr>
<td>Accelerated</td>
<td>40°C/75% RH Horizontal</td>
<td>(X) (X) X - - - - -</td>
</tr>
</tbody>
</table>

Summary of Leachable Studies:
Semi-volatile and volatile leachables were tracked for 60 months during the stability study. Test data up to 24 months was provided in the current submission. A summary of quantifiable leachable compounds detected in Belimumab SC drug product is shown in the table below.

Table 6. Quantifiable leachable results for Belimumab SC drug product

<table>
<thead>
<tr>
<th>Compound</th>
<th>Maximum Human Exposure (mcg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(b) (b)</td>
</tr>
</tbody>
</table>

3 Studies Submitted

3.1 Studies Reviewed

<table>
<thead>
<tr>
<th>STUDY</th>
<th>STUDY NUMBER:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belimumab (GSK1550188) – Summary of leachables stability data generated on Benlysta SC DP</td>
<td>2017N313742</td>
</tr>
</tbody>
</table>
11 Integrated Summary and Safety Evaluation

This review provides a safety assessment of potential leachables from the container closure system for Benlysta SC drug product, based on data submitted by the Sponsor and other available information. The Sponsor is seeking approval for the drug product at a dose of 200 mg to be delivered once weekly via a subcutaneous injection from either a single-dose autoinjector or a single-dose prefilled syringe in a 1 mL volume. Of note, although the drug product is delivered once weekly, any comparisons made in this evaluation are based on acceptable levels per day. Adjustments for dosing intervals were not made in order to provide a conservative safety assessment. In general, for leachable evaluations, any nonmetal compound with expected patient exposure below the PQRI thresholds of (4) mcg/day (for compounds lacking genotoxic potential and irritant potential) and (4) mcg/day (for compounds with genotoxic potential) was considered qualified for safety regardless of the available nonclinical data.¹

Leachables Assessment

A leachables assessment was conducted on three batches of Benlysta SC DP. Test points up to 24 months were provided. The drug product was stored in a horizontal orientation under ICH stability conditions.

Leachable studies identified (4) at quantifiable levels in Belimumab SC drug product. The Sponsor stated that no volatile leachable compounds were observed above the PQRI threshold of (4) mcg/day.

was added to the container closure system to maintain its correct operation. The Sponsor stated that the maximum amount of detected in Belimumab batches to date was equivalent to a patient exposure of mcg/day. Data available in the peer-reviewed literature indicate were negative for genotoxicity.²,³ all were negative for mutagenic potential based on the Ames Assay. were positive for clastogenic effects in an in vitro mammalian assay in mouse lymphoma cells, but when further evaluated in an in vivo rodent bone marrow cytogenetic assay, were considered to be clastogenic. Further, while general toxicity data for the subcutaneous administration of were not available,

For a 60 kg person, mcg per syringe is equivalent to mcg/kg ng/kg). This results in a 9-fold safety margin for the level of ¹ Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. Product Quality Research Institute, August 2008
per syringe detected in the Belimumab batches. Based on this information, the safety of (b)(4) is considered qualified.

Leachable levels of (b)(4) were detected (b)(4) is considered qualified for safety based on the respective low estimated total daily intakes from the leachable studies.

The Sponsor stated that (b)(4) was detected at levels in samples equivalent to a patient exposure of (b)(4) mcg/day. (b)(4) that is represented in the normal human diet. Dietary intake of (b)(4) has been reported as (b)(4) mg per day in subjects with (b)(4). Based on the large margin compared to dietary intake, the level of (b)(4) in Belimumab SC drug product is considered qualified from the nonclinical perspective.

Overall, there appear to be no nonclinical safety concerns for the Belimumab SC drug product as described in the leachable studies for the primary container closure system.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRETT R JONES
06/18/2017

ANDREW C GOODWIN
06/18/2017
I concur
PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: BLA 761043
Supporting document/s: SDN#1
Applicant's letter date: September 22, 2016
CDER stamp date: September 22, 2016
Product: BENLYSTA® (Belimumab)
Indication: Systemic lupus erythematosus
Applicant: Human Genome Sciences (GSK)
Review Division: Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer: Brett Jones, PhD
Supervisor/Team Leader: Timothy Robison, PhD, DABT
Division Director: Badrul Chowdhury, MD, PhD
Project Manager: Jessica Lee

Template Version: September 1, 2010
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1 Executive Summary

1.1 Introduction

BENLYSTA® is currently approved for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The recommended dosage regimen is 10 mg/kg intravenously (IV) at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

For the current submission, the Sponsor has proposed BENLYSTA\(^{(b)(d)}\) (200 mg) be administered subcutaneously (SC) once weekly in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The application includes a 200 mg (in 1 mL) single-dose autoinjector and a 200 mg (in 1 mL) single-dose prefilled syringe for self-administration. The Sponsor submitted several nonclinical pharmacology or toxicology studies to support the current application. A 4-week bridging study in cynomolgus monkeys was conducted to support the new proposed subcutaneous route of administration.

1.2 Brief Discussion of Nonclinical Findings

There is a complete nonclinical program for belimumab under BLA 125370, which the Sponsor cross-referenced in support of the current application. Refer to the Pharmacology and Toxicology Review of BLA 125370 (dated November 24, 2010) for further information on general toxicology and reproductive toxicology studies with belimumab administered by the intravenous route.

A 4-week GLP-compliant local tolerance study in cynomolgus monkeys (with 4-week recovery period) was conducted to support the new proposed subcutaneous route of administration by assessing toxicity at subcutaneous injection sites.

In the 4-week monkey study, cynomolgus monkeys received belimumab by subcutaneous administration at a dose of 1000 mg/animal once every 2 weeks for a total of 3 doses (on Days 1, 15, and 29). The proposed clinical formulation of the SC drug product was used in this study. Following the final dose on Day 29, animals were observed for a 4-week recovery period. This study was limited to an assessment of local toxicity of the skin surrounding the subcutaneous injection sites collected 24-hr after the last dose (Day 29). There were no adverse findings in skin samples collected from injection sites. There was no evidence of latent toxicity on Day 57.

There are no nonclinical safety concerns for administration of belimumab by the subcutaneous route.
1.3 Recommendations

1.3.1 Approvability
BLA 761043 is recommended for approval from the nonclinical perspective. The label should be modified as shown below.

1.3.2 Additional Non Clinical Recommendations
None.

1.3.3 Labeling
For this submission, the Sponsor provided a label for BENLYSTA \(^{(b)}\) identical to that approved for BENLYSTA by DPARP on January 2017. Specifically, the label incorporates information in compliance with the Pregnancy and Lactation Labeling Rule (PLLRR). Refer to the Pharmacology and Toxicology Review of BLA 125370 (dated August 18, 2016) for further information on the PLLR conversion of BENLYSTA\(^{®}\) (belimumab).

Recommended labeling for Highlights of Prescribing Information, Sections 8.1 (Pregnancy), 8.2 (Lactation), and 13 (Nonclinical Toxicology) in the proposed product label are shown below.

The Reviewer’s recommended labeling is shown below. Additions are shown as underlined text and deletions are shown as strikethrough text with respect to the Sponsor’s proposed BENLYSTA \(^{(b)}\) label.

INDICATIONS AND USAGE in the HIGHLIGHTS OF PRESCRIBING INFORMATION
BENLYSTA \(^{(b)}\), a B-lymphocyte stimulator (BLyS)-specific inhibitor, indicated for:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BENLYSTA \(^{(b)}\) during pregnancy. Healthcare professionals are encouraged to register patients by calling 1-877-681-6296.

Risk Summary
Limited data on use of belimumab in pregnant women, from observational studies, published case reports, and postmarketing surveillance, are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with SLE \[see Clinical Considerations]. Monoclonal antibodies, such as belimumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the
in utero-exposed infant [see Clinical Considerations]. In an animal combined embryofetal and pre- and post-natal development study with monkeys that received belimumab by intravenous administration, there was no evidence of embryotoxicity or fetal malformations with exposures approximately 8 times the exposure at the maximum recommended human dose (MRHD). Belimumab-related findings in monkey fetuses and/or infants included reductions of B-cell counts, reductions in the density of lymphoid tissue B-lymphocytes in the spleen and lymph nodes, and altered IgG and IgM titers. The no-adverse-effect-level (NOAEL) was not identified for these findings; however, they were reversible within 3 to 12 months after the drug was discontinued [see Data]. Based on animal data and the mechanism of action of belimumab, the immune system in infants of treated mothers may be adversely affected. It is unknown, based on available data whether immune effects, if identified, are reversible [see Clinical Pharmacology (12.1)].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk:
Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, spontaneous abortion, and intrauterine growth restriction. Maternal lupus nephritis increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal anti-phospholipid antibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

Fetal/Neonatal Adverse Reactions:
Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to BENLYSTA in utero. Monitor an infant of a treated mother for B-cell reduction and other immune dysfunction [see Warnings and Precautions (5.5)].

Data
Animal Data:
In a combined embryo-fetal and pre- and post-natal development study, pregnant cynomolgus monkeys received belimumab at intravenous doses of 0, 5, or 150 mg/kg every 2 weeks from confirmation of pregnancy at Gestation Days (GD) 20 to 22, throughout the period of organogenesis (up to approximately GD 50), and continuing to either the day of scheduled cesarean section (GD 150 [late third trimester]) or the day of parturition. There was no evidence of maternal toxicity, embryotoxicity, or teratogenicity at exposure approximately 8 times the exposure at the MRHD of 200 mg subcutaneously (on an AUC basis with maternal intravenous doses up to 150 mg/kg).
Belimumab-related findings in mothers included reductions of immature and mature B-cell counts and in fetuses and/or infants included reductions of immature and mature B-cell counts, reductions in the density of lymphoid tissue B-lymphocytes in the spleen and lymph nodes, reduced spleen weights, increased IgG titers, and reduced IgM titers. B-cell counts in infant monkeys exposed to belimumab in utero recovered by 3 months of age and in mothers after 1 year. IgG and IgM levels in infant monkeys recovered by 6 months of age and the reductions in B-lymphocytes in the lymph nodes and spleen were reversed by 1 year of age. Belimumab crossed the placenta, as it was detected in fetal cord blood and amniotic fluid on GD 150.

8.2 Lactation
Risk Summary
No information is available on the presence of belimumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Belimumab was detected in the milk of cynomolgus monkeys; however, due to species-specific differences in lactation physiology, animal data may not predict drug levels in human milk. Maternal IgG is known to be present in human milk. If belimumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to belimumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of BENLYSTA to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BENLYSTA, and any potential adverse effects on the breastfed child from BENLYSTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential
Contraception
Following an assessment of benefit versus risk, if prevention of pregnancy is warranted, females of reproductive potential should use effective contraception during treatment and for at least 4 months after the final treatment.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of belimumab.

Effects on male and female fertility have not been directly evaluated in animal studies.
2 Drug Information

2.1 Drug

CAS Registry Number
356547-88-1

Trade Name
BENLYSTA®

Generic Name
Belimumab

Molecular Formula/Molecular Weight
147 KDaltons

Structure or Biochemical Description
Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

Pharmacologic Class
BENLYSTA® (belimumab) is a human IgG1\(\lambda\) monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B)

2.2 Relevant INDs, NDAs, BLAs and DMFs

BLA 125370 (Belimumab, GSK)

2.3 Drug Formulation

Each prefilled syringe of belimumab drug product is intended to deliver 200 mg of sterile liquid belimumab. The composition per dose is 200 mg/mL belimumab in a formulation containing histidine, sodium chloride, arginine hydrochloride and polysorbate 80 at a pH of 6.0 (see table below).
Belimumab injection for subcutaneous use (200 mg/1.0 mL) is supplied as a single-use, sterile liquid drug product in two formats. The formats include a prefilled syringe assembled with additional functional components to create an autoinjector, referred to as belimumab drug product (DP) in autoinjector, 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 subcutaneous use. The belimumab DP container closure consists of a 1 mL long, Type I glass syringe with staked needle (27G, ½ inch), rubber plunger stopper, and a rigid needle shield.
(Excerpt from Sponsor's submission)

Figure 1. Appearance of the Belimumab drug product prefilled syringe container closure

Figure 1 Appearance of the Belimumab Drug Product Prefilled Syringe Container Closure

(Excerpt from Sponsor's submission)

Figure 2. External appearance of the Belimumab drug product in autoinjector (before use)

Figure 2 External Appearance of the Belimumab Drug Product in Autoinjector (Before Use)
2.4 Comments on Novel Excipients

Benlysta is currently marketed as 120 mg or 400 mg lyophilized powder for concentrate for solution for intravenous infusion. After reconstitution, the solution contains 80 mg belimumab per mL. The approved formulation contains citric acid, sodium citrate, sucrose (80 mg/mL), and polysorbate 80.

The composition of the proposed Benlysta drug product for subcutaneous use is provided above. There are no safety concerns with the excipients in the proposed Benlysta subcutaneous formulation.

2.6 Proposed Clinical Population and Dosing Regimen

BENLYSTA® is currently approved for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The recommended dosage regimen is 10 mg/kg intravenously (IV) at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

For this submission, the Sponsor has proposed BENLYSTA (200 mg) be administered subcutaneously (SC) once weekly in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The application includes a 200 mg (in 1 mL) single-dose autoinjector and a 200 mg (in 1 mL) single-dose prefilled syringe for self-administration.
2.7 Regulatory Background

BENLYSTA® was approved for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy on March 9, 2011.

3 Studies Submitted

3.1 Studies Reviewed

There is a complete nonclinical program for belimumab under BLA 125370, which the Sponsor cross-referenced in support of the current application. However, several nonclinical pharmacology or toxicology studies were submitted in support of the current application.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>STUDY NUMBER:</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY PHARMACOLOGY</td>
<td></td>
</tr>
<tr>
<td>Binding specificity of belimumab to BLyS compared to</td>
<td>2010n110702/</td>
</tr>
<tr>
<td>members of TNF ligand superfamily</td>
<td>HG19399.SLE.0.055</td>
</tr>
<tr>
<td>Evaluation of the Fc-mediated functions of belimumab</td>
<td>2011n115953/</td>
</tr>
<tr>
<td></td>
<td>HG19399.SLE.0.056</td>
</tr>
<tr>
<td>Evaluation of the Fc-mediated functions of belimumab</td>
<td>2012n155096/</td>
</tr>
<tr>
<td>in primary CD14+ monocytes and in vitro binding to</td>
<td>HG19399.SLE.0.058</td>
</tr>
<tr>
<td>FcγRIIIa</td>
<td></td>
</tr>
<tr>
<td>PK/ADME</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetics of belimumab in BALB/c mice following a single subcutaneous administration</td>
<td>2012n155097/</td>
</tr>
<tr>
<td></td>
<td>HG19399.SLE.0.059</td>
</tr>
<tr>
<td>GENERAL TOXICOLOGY</td>
<td></td>
</tr>
<tr>
<td>A 4-week subcutaneous injection local tolerance study with belimumab in Cynomolgus monkeys with a 4-week recovery period</td>
<td>2012n155098/</td>
</tr>
<tr>
<td></td>
<td>8246530</td>
</tr>
</tbody>
</table>

3.3 Previous Reviews Referenced

1. Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010 (BLA general review)

2. Pharmacology and Toxicology Review of BLA 125370 dated August 18, 2016 (PLLR conversion)
4 Pharmacology

4.1 Primary Pharmacology

The Sponsor provided 3 pharmacology studies in the current submission. For a review of primary pharmacology studies, see the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.

According to the Sponsor’s report, belimumab is a recombinant, human IgG1\(\lambda\) monoclonal antibody developed to specifically bind and antagonize 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.

**Study Title: Binding specificity of belimumab to BLyS compared to members of TNF ligand superfamily (Study no. 2010n110702/ HG19399.SLE.0.055)**

The specificity of belimumab binding to B Lymphocyte Stimulator (BLyS) was examined by testing the ability of various other TNF ligand family members to bind to belimumab using the BIACore technology. The human TNF ligand family members selected for screening were APRIL, the ligand with closest homology to BLyS, as well as several other family members that are involved in immune regulation: TNF-\(\alpha\), TNF-\(\beta\), LIGHT, FasL, and TL1-A.

Belimumab binding to various TNF ligands was assessed by flowing ligands over a belimumab derivatized flowcell at a constant temperature of 25°C. TNF ligands were injected at 2 concentrations (4.9 nM and 49 nM) over both belimumab derivatized flow cells at a rate of 25 \(\mu\)L/minute for 60 sec.

The BIACore experiments demonstrated that belimumab only specifically bound to human BLyS as no binding to several other TNF ligands were observed including APRIL, TNF-\(\alpha\), TNF-\(\beta\), LIGHT, FasL, and TL1-A, even when tested at higher concentrations (49 nM).

**Study Title: Evaluation of the Fc-mediated functions of belimumab (Study no. 2011n115953/ HG19399.SLE.0.056)**

The aim of this investigation was to characterize and define the Fc-mediated binding to neonatal Fc receptor (FcRn) and Fc-mediated immune effector functions of belimumab. Binding of belimumab to FcRn was assessed with FcRn covalently coupled to a BIACore CM5 biosensor chip. The ability of belimumab to induce Fc mediated immune effector functions of antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) was determined. ADCC was assessed with a flow cytometry-based method using primed NK cells as effector cells and target cells expressing BLyS (cell line U937, ATCC) or binding soluble BLyS (cell line ST486,
ATCC) and labeled with Cell Tracker Green. The effector to target cell ratio was 8:1. Propidium iodide was added and viability of Cell Tracker Green labeled target cells was assessed by flow cytometry. The monocyctic cell line, U937, which expresses BLyS, was used to assess CDC. Cells were incubated with belimumab ± 10% fresh human serum. Following the incubation, propidium iodine was added and cell viability was assessed by flow cytometry.

The $K_{D1}$ values for the binding of belimumab, raxibacumab, and rituximab to FcRn are shown in the table below. The Measured $K_{D1}$ values were 618, 590, and 318 nM for belimumab, raxibacumab, and rituximab, respectively. The binding affinity of belimumab to FcRn was comparable to raxibacumab and rituximab. These values are similar to the values reported for both fully human, humanized and chimeric monoclonal antibodies which ranged from 508 to 1237 nM.

(Excerpt from Sponsor’s submission)

**Table 2. $K_{D1}$ values for human monoclonal antibodies: belimumab, raxibacumab, and rituximab**

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>belimumab</th>
<th>raxibacumab</th>
<th>rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>658</td>
<td>728</td>
<td>336</td>
</tr>
<tr>
<td></td>
<td>763</td>
<td>664</td>
<td>351</td>
</tr>
<tr>
<td></td>
<td>431</td>
<td>378</td>
<td>266</td>
</tr>
<tr>
<td>Mean$^2$</td>
<td>618</td>
<td>590</td>
<td>318</td>
</tr>
<tr>
<td>SD</td>
<td>170</td>
<td>187</td>
<td>45</td>
</tr>
</tbody>
</table>

$^1$ $K_{D1}$ values = $k_1/d_{1}$.

$^2$ Represents mean of 3 independent determinations.

The Sponsor’s report stated that belimumab binds to soluble BLyS but not to membrane BLyS. Therefore, the results from the ADCC and CDC assays confirmed that belimumab does not mediate Fc effector functions.

**Study Title: Evaluation of the Fc-mediated functions of belimumab in primary CD14+ monocytes and in vitro binding to FcγRIIIa (Study no. 2012n155096/HG19399.SLE.0.058)**

The aim of this investigation was to assess the ability of the Fc region of belimumab to bind FcγRIIIa and its ability to induce effector functions of ADCC and CDC was determined. Binding of belimumab to FcγRIIIa was assessed with FcγRIIIa coupled to a BIAcore CM5 biosensor chip. ADCC was assessed in a similar manner as described above using NK cells as effector cells and primary human CD14+ monocytes, expressing BLyS, as target cells.

CDC was assessed in a similar manner as described above using human CD14+ monocytes. In order to prevent binding to human FcγR and still retain complement binding the Fc region of the antibodies were converted into murine Fc gamma 1
(mIgG1) isotype which bind complement but do not bind to human monocyte Fcγ receptors.

Cell surface expression of the membrane form of BLyS on U937 cells and human CD14+ monocytes was confirmed by flow cytometry analysis.

The $K_D$ values for the binding of belimumab, rituximab, and IgG1-κ to FcyRIIIa were 1.79, 2.09, and 2.68 μM, respectively (see table below). IgG4 binding was too low for an accurate measurement. These values indicate that belimumab displays similar affinity to the low affinity FcyRILla receptor as observed for the other IgG1 classes tested. These values are consistent with ~1 μM $K_D$ value previously reported for monomeric human immunoglobulins.

(Excerpt from Sponsor’s submission)

### Table 3. FcγRIIIa $K_D$ values for human monoclonal antibodies: belimumab, rituximab, IgG1-κ, and IgG4

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>belimumab</th>
<th>rituximab</th>
<th>IgG-κ</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>1.79E-06</td>
<td>2.09E-06</td>
<td>2.68E-06</td>
<td>nd²</td>
</tr>
<tr>
<td>SE</td>
<td>0.041E-06</td>
<td>0.035E-06</td>
<td>0.036E-06</td>
<td>nd²</td>
</tr>
</tbody>
</table>

$^1$ $K_D$ values determined from EC50 analysis of Figure 3-1 data.

$^2$ nd = EC50 value not determined, failed to calculate a curve fit.

The results from the CDC and ADCC assays confirmed that belimumab did not mediate these effector functions as belimumab binds to soluble BLyS, but not to membrane BLyS. Another anti-BLyS antibody, 9B6, known to bind to cell surface BLyS was able to mediate both CDC and ADCC activity. The concentration of belimumab (66 nM) used for analysis of CDC and ADCC effector functions were 200 times the Kd.

### 4.2 Secondary Pharmacology

For a review of secondary pharmacology studies, see the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.

### 4.3 Safety Pharmacology

For a review of safety pharmacology studies, see the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.
5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

For a review of PK/ADME studies, see the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.

Absorption:

Study Title: Pharmacokinetics of belimumab in BALB/c mice following a single subcutaneous administration (Study no. 2012n155097/ HG19399.SLE.0.059)

Methods: The aim of this investigation was to compare the pharmacokinetics (PK) of belimumab in BALB/c mice following a single subcutaneous (SC) injection of belimumab liquid formulation, an aged belimumab liquid sample and deamidated belimumab, and to demonstrate the PK comparability between belimumab liquid formulation and the aged belimumab liquid sample.

(Excerpt from Sponsor’s submission)

Table 4. Group assignments and dosing information

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Animals</th>
<th>Treatment</th>
<th>SC Dose (mg/kg)</th>
<th>Dose Concentration (mg/mL)</th>
<th>Dose Volume (μL)¹</th>
<th>Body Weight (g)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 females</td>
<td>Reference belimumab liquid formulation</td>
<td>10</td>
<td>1</td>
<td>200 ± 10</td>
<td>20.1 ± 1.4</td>
</tr>
<tr>
<td>2</td>
<td>30 females</td>
<td>Aged belimumab liquid sample</td>
<td>10</td>
<td>1</td>
<td>198 ± 6</td>
<td>19.8 ± 0.8</td>
</tr>
<tr>
<td>3</td>
<td>30 females</td>
<td>Deamidated belimumab</td>
<td>10</td>
<td>1</td>
<td>201 ± 8</td>
<td>20.4 ± 1.1</td>
</tr>
</tbody>
</table>

¹ Mean ± standard deviation (SD) for the individual mice administered the test articles.

Results: It was noted that BALB/c mice are not a pharmacologically relevant species for belimumab. No significant differences in PK parameters were observed for the reference belimumab liquid formulation and aged belimumab sample following a single 10 mg/kg SC injection in mice.

Following a single 10 mg/kg SC dose of reference belimumab liquid formulation or aged belimumab liquid sample, the mean $T_{\text{max}}$ was 1.5 days for the reference formulation and 1.8 days for the aged sample. Immunogenicity analyses showed a correlation between the presence of anti-belimumab antibodies and the decreased concentrations of belimumab. There were a higher incidence and higher level of anti-belimumab antibodies in mice dosed with the deamidated product. Serum concentrations of the deamidated belimumab dropped below the LLOQ (< 100 ng/mL) by 10 days postdose, and correlated with the presence of anti-drug antibodies (ADA). According to the Sponsor’s report, the ADA can either promote a much faster clearance of the belimumab-ADA complex or neutralize the BLyS binding activity of belimumab making it undetectable in the PK assay. PK parameters for the deamidated product other than $T_{\text{max}}$ and $C_{\text{max}}$ could not be reliably determined.
Table 5. Mean (95% CI) PK parameters following a single 10 mg/kg SC dose of reference belimumab liquid formulation, the aged belimumab liquid sample or deamidated belimumab in mice

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Reference Product</th>
<th>Group 2 Aged Product</th>
<th>Group 3 Deamidation Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{\text{max}} ) (days)</td>
<td>Estimate 1.54 1.78 2.00</td>
<td>( 95 % \text{ CI} ) (1.13, 1.95) (1.53, 2.02) -</td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (( \mu \text{g/mL} ))</td>
<td>Estimate 139 136 138</td>
<td>( 95 % \text{ CI} ) (125, 153) (128, 143) (133, 143)</td>
<td></td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) (( \mu \text{g} \cdot \text{day/mL} ))</td>
<td>Estimate 1229 1128 -</td>
<td>( 95 % \text{ CI} ) (985, 1474) (1009, 1247) -</td>
<td></td>
</tr>
<tr>
<td>( t_{1/2,\text{abs}} ) (days)</td>
<td>Estimate 0.39 0.51 -</td>
<td>( 95 % \text{ CI} ) (0.21, 0.56) (0.37, 0.64) -</td>
<td></td>
</tr>
<tr>
<td>( t_{1/2,\text{term}} ) (days)</td>
<td>Estimate 4.94 4.34 -</td>
<td>( 95 % \text{ CI} ) (3.38, 6.50) (3.52, 5.15) -</td>
<td></td>
</tr>
<tr>
<td>CL/F (mL/day/kg)</td>
<td>Estimate 8.55 8.75 -</td>
<td>( 95 % \text{ CI} ) (6.85, 10.25) (7.83, 9.67) -</td>
<td></td>
</tr>
<tr>
<td>V/F (mL/kg)</td>
<td>Estimate 60.90 54.73 -</td>
<td>( 95 % \text{ CI} ) (50.24, 71.56) (48.36, 61.09) -</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: \( t_{\text{max}} \), time to the maximum serum drug concentration; \( C_{\text{max}} \), maximum serum drug concentration; \( \text{AUC}_{0-\infty} \), area under the serum drug concentration-time curve from time 0 to infinite time; \( t_{1/2,\text{abs}} \), absorption half-life; \( t_{1/2,\text{term}} \), terminal elimination half-life; CL/F, apparent clearance; V/F, apparent volume of distribution; CI, confidence interval.

1 Only observed \( C_{\text{max}} \) and \( t_{\text{max}} \) were reported and other PK parameters can’t be reliably estimated.
6 General Toxicology

6.1 Single-Dose Toxicity
See the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.

6.2 Repeat-Dose Toxicity
The Sponsor conducted a comprehensive program of toxicology studies using the intravenous route. See the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.

Study title: An 8-week (4-week treatment period and 4-week recovery period) subcutaneous injection local tolerance study with belimumab in Cynomolgus monkeys

<table>
<thead>
<tr>
<th>Study no.</th>
<th>2012n155098/ 8246530</th>
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<tbody>
<tr>
<td>Study report location</td>
<td>EDR</td>
</tr>
<tr>
<td>Conducting laboratory and location</td>
<td></td>
</tr>
<tr>
<td>Date of study initiation</td>
<td>June 2, 2011 (start of dosing)</td>
</tr>
<tr>
<td>GLP compliance</td>
<td>Yes</td>
</tr>
<tr>
<td>QA statement</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug, lot #, and % purity</td>
<td>Belimumab; Lot No. 10TA0601; Purity: 99.4%</td>
</tr>
</tbody>
</table>

Key Study Findings

- In a 4-week subcutaneous local tolerance study, monkeys (4 males/group) received belimumab at a dose of 1000 mg/animal Q2W for a total of 3 doses (on Days 1, 15, and 29). Animals were observed for a 4-week recovery period following the final dose on Day 29. The proposed clinical formulation of the SC drug product was used in this study.
- A slight decrease in in B cell lymphocyte counts was observed in the 1000 mg/animal/dose group relative to controls at the end of the treatment and recovery periods. This finding was considered due to the pharmacological activity of the test article.
- Dermal irritation scoring was conducted daily. Slight to moderate edema was observed in 2 males in the 1000 mg/animal/dose group on Day 1 of the dosing phase at the 2 hr postdose interval. These findings were not considered adverse.
- The tissue examination for each animal was limited to a skin sample (approximately 4 mm in diameter) collected, approximately 24 hr after the final dose (Day 29), by punch biopsy in the area surrounding the final injection. Skin samples were stained with hematoxylin and eosin, and evaluated. No adverse findings were identified in subcutaneous injection sites.
- There was no evidence of latent toxicity at the injection sites on Day 57.
Methods

- **Doses:** 0 and 1000 mg/animal/dose
- **Frequency of dosing:** Once every 2 weeks (Days 1, 15, and 29)
- **Route of administration:** Subcutaneous
- **Dose volume:** 5 mL/animal/dose
- **Formulation/Vehicle:** 0.65 mg/mL L-histidine, 1.2 mg/mL L-histidine monohydrochloride, 6.7 mg/mL sodium chloride, 5.3 mg/mL L-arginine hydrochloride, and 0.1 mg/mL polysorbat e 80, pH 6.0.
- **Species/Strain:** Cynomolgus monkeys
- **Number/Sex/Group:** 4 males/group
- **Age:** Approximately 3-4 years old at start of treatment
- **Weight:** 3.4-3.6 kg
- **Satellite groups:** None
- **Unique study design:** None
- **Deviation from study protocol:** Minor deviations did not affect the integrity of the study

(Excerpt from Sponsor’s submission)

**Table 6. Study design of the local tolerance monkey study with a 4-week treatment period and 4-week recovery period**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Males</th>
<th>Dose Level (mg/animal/dose)</th>
<th>Dose Volume (mL/animal/dose)</th>
<th>Dose Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Control)</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2 (Belimumab)</td>
<td>4</td>
<td>1000</td>
<td>5</td>
<td>200</td>
</tr>
</tbody>
</table>

*Animals in Group 1 received the vehicle control article [0.65 mg/mL L-histidine, 1.2 mg/mL L-histidine monohydrochloride, 6.7 mg/mL sodium chloride, 5.3 mg/mL L-arginine hydrochloride, and 0.1 mg/mL polysorbat e 80, pH 6.0] only.*

The study incorporated standard evaluations including clinical observations, dermal irritation, body weights, clinical pathology, urinalysis, histopathology/skin punch biopsy, toxicokinetics, and immunophenotyping.

**Observations and Results**

**Mortality**

Animals were checked twice daily (a.m. and p.m.) for mortality, abnormalities, and signs of pain and distress.

There were no unscheduled deaths in the study.

**Clinical Signs**

Cageside observations were done once daily during the predose and dosing phases. In addition, cageside observations were made on each dosing day approximately 30 minutes and 2 hrs postdose. Detailed observations were done four times during the
predose phase, before dosing on Day 1 of the dosing phase, weekly thereafter (based on Day 1), and on the last day of the in-life portion of the study.

Clinical observations of hunched posture (one male) and liquid (two males) or nonformed (two males) feces were observed during the 4-week treatment period and 4-week recovery period.

One male animal in the 1000 mg/animal/dose group (Animal no. #108595) was examined by a veterinarian on Day 12 of the dosing period due to a sore and scab on the right shoulder. According to the Sponsor’s report, the animal had presented earlier during the predose period with purulent discharge in the same site, apparently related to suturing of the area. The animal was treated with an antibiotic. This observation was not considered test article related.

**Table 7. Clinical signs observed for monkeys during the 4-week treatment period and 4-week recovery period (number of animals)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Males (mg/animal/dose)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1000</td>
</tr>
<tr>
<td>No. examined</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Appearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hunched posture</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Excretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Feces, liquid</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>- Feces, nonformed</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Dermal irritation scoring was evaluated on each dosing day prior to dosing and approximately 30 minutes and 2 hr postdose. The dose site was also observed once daily on nondosing days through Day 28 of the dosing period.

Dermal irritation scores at the dosing site are summarized in the table below. Slight to moderate edema was observed in 2 males in the 1000 mg/animal/dose group on Day 1 of the dosing phase at the 2 hr postdose interval. These findings were not considered adverse.

Clinical observations found no evidence of latent toxicity at injection sites of Day 57.
Body Weights

Body weights were recorded during the predose phase, before dosing on Day 1, weekly thereafter (based on Day 1), and on the last day of the in-life portion of the study.

No treatment-related effects on body weight were observed.

Hematology

Blood samples were collected via a femoral vein for hematology analyses from animals fasted overnight. Samples were collected twice during the predose phase and on Days 19, 33, and 57 of the dosing phase.

No treatment-related effects on hematology parameters were observed.
Clinical Chemistry
Blood samples were collected via a femoral vein for clinical chemistry analyses from animals fasted overnight. Samples were collected twice during the predose phase and on Days 19, 33, and 57 of the dosing phase.

No treatment-related effects on clinical chemistry parameters were observed.

Urinalysis
Urine samples were collected from animals fasted overnight for urinalysis. Samples were collected once during the predose phase and on Days 19, 33, and 57 of the dosing phase.

No significant treatment related effects on urinalysis parameters were observed.

Histopathology
Adequate Battery
The tissue examination for each animal was limited to a skin sample (approximately 4 mm in diameter) collected, approximately 24 hr after the final dose (Day 29), by punch biopsy from the dosing site surrounding the final injection. All animals were returned to the stock colony on Day 57 of the dosing phase.

Peer Review
A peer review was not conducted.

Histological Findings
Skin samples were collected from anesthetized animals once approximately 24 hr after the final dose (Day 29). Samples were collected from the dosing site surrounding the final injection. One sample was collected from each animal with a skin punch and stored in 10% neutral-buffered formalin. Skin samples were stained with hematoxylin and eosin, and evaluated by a board-certified pathologist.

Minimal infiltration of lymphocytes/macrophages in the skin subcutis was observed for two males in the 1000 mg/animal/dose group at the end of the treatment period. These findings were not considered adverse or dose-limiting.
Table 9. Histopathological findings at the dose site in monkeys at the end of the 4-week treatment period

<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>No. examined</td>
<td>4</td>
</tr>
<tr>
<td>Skin/Subcutis</td>
<td></td>
</tr>
<tr>
<td>- Infiltrate, lymph/macro., subcutis</td>
<td>0/4</td>
</tr>
<tr>
<td>minimal</td>
<td>0</td>
</tr>
<tr>
<td>- Inflammation, acute/subacute</td>
<td>0/4</td>
</tr>
<tr>
<td>slight</td>
<td>4</td>
</tr>
</tbody>
</table>

Toxicokinetics

Toxicokinetic analysis was done by the Sponsor, with $C_{\text{max}}$ and $C_{\text{min}}$ as the only toxicokinetic parameters calculated for individual animals as serum samples were only collected at peak and trough times following each dose administration.

All four animals receiving SC doses of belimumab at 1000 mg (244 to 292 mg/kg) exhibited systemic exposure ($C_{\text{max}}$) to belimumab. Samples collected prior to administration of the first dose had no measurable serum belimumab concentrations.

Immunophenotyping

Blood samples were collected twice during the predose phase and on Days 33 and 57 of the dosing phase via a femoral vein.

Immunophenotyping data for the control and 100 mg/animal/dose groups is summarized below. A slight decrease in absolute B cell lymphocyte counts was observed in the 1000 mg/animal/dose group relative to controls at the end of the treatment and recovery periods. This finding was considered due to the pharmacological activity of the test article and was not considered adverse. This finding is monitorable in a clinical setting.

Table 10. Immunophenotyping data in monkeys at the end of the treatment and recovery periods

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day</th>
<th>Males (mg/animal/dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B lymphocytes $10^3/\mu$L</td>
<td>33</td>
<td>2.08</td>
</tr>
<tr>
<td></td>
<td>57(R)</td>
<td>1.88</td>
</tr>
<tr>
<td>B lymphocytes %</td>
<td>33</td>
<td>29.55</td>
</tr>
<tr>
<td></td>
<td>57(R)</td>
<td>30.05</td>
</tr>
</tbody>
</table>

(p < 0.05).
7 Genetic Toxicology
Genetic toxicity studies are not required for biologic products derived by recombinant DNA technology. See the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.

8 Carcinogenicity
See the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.

9 Reproductive and Developmental Toxicology
For a review of reproductive toxicity studies, see the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.

10 Special Toxicology Studies
See the Pharmacology and Toxicology Review of BLA 125370 dated November 24, 2010.

11 Integrated Summary and Safety Evaluation
BENLYSTA® is a B-lymphocyte stimulator (BLyS)-specific inhibitor currently approved for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. The recommended dosage regimen is 10 mg/kg intravenously (IV) at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

For the current submission, the Sponsor has proposed BENLYSTA® (200 mg) be administered subcutaneously (SC) once weekly in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The application includes a 200 mg (in 1 mL) single-dose autoinjector and a 200 mg (in 1 mL) single-dose prefilled syringe for self-administration.

A 4-week local tolerance study in cynomolgus monkeys (with 4-week recovery period) was conducted to support the new proposed subcutaneous route of administration.

Assessment of Local Toxicity at the Subcutaneous Injection Site: In the 4-week monkey study, cynomolgus monkeys received belimumab by subcutaneous administration at a dose of 1000 mg/animal once every 2 weeks for a total of 3 total doses (on Days 1, 15, and 29). The proposed clinical formulation of the SC drug product was used in this study. Animals were observed for a 4-week recovery period following the final dose on Day 29. A slight decrease in B cell lymphocyte counts was observed in the 1000 mg/animal/dose group relative to controls at the end of the treatment and
recovery periods, which was attributed to the pharmacological activity of the test article. Dermal irritation scoring conducted daily. Slight to moderate edema was observed in 2 males in the 1000 mg/animal/dose group on Day 1 of the dosing phase at the 2 hr postdose interval. These findings were not considered adverse. The tissue examination for each animal was limited to a skin sample (approximately 4 mm in diameter) collected by punch biopsy from the dosing site surrounding the final injection. Skin samples were collected from anesthetized animals once approximately 24 hr after the final dose (Day 29). Skin samples were stained with hematoxylin and eosin, and evaluated. No adverse findings were identified in subcutaneous injection sites. There was no evidence of latent toxicity at injection sites on Day 57.

There are no nonclinical safety concerns for administration of belimumab by the subcutaneous route.

There is a complete nonclinical program for belimumab. Refer to the Pharmacology and Toxicology Review of BLA 125370 (dated November 24, 2010) for further information on general toxicology and reproductive toxicology studies with belimumab administered by the intravenous route.

Toxicology studies to support the chronic use of belimumab included 4-week (0, 5, 15, and 50 mg/kg/week) and 6-month (0, 5, 15 and 50 mg/kg every two weeks) intravenous (IV) studies in cynomolgus monkeys. In the 4-week study, the target organs of toxicity were the injection site, lymph system, spleen and peripheral blood (B-cell depletion). In the 6-month IV study, the target organs of toxicity were the spleen (lymphoid depletion and hyperplasia), mesenteric lymph node (lymphoid depletion and hyperplasia), GI tract (lymphoid hyperplasia), kidney (regeneration of tubule and glomerular thickening), pancreas (mononuclear infiltration and fibrosis), and thyroid (mononuclear infiltration, follicular degeneration) and peripheral blood (B-cell decreased). Vasculitis was observed in a number of organs including the kidney, sciatic nerve, cervix, and heart with low incidence in females in the high-dose group (50 mg/kg). Most of these findings were considered as exaggerated pharmacological effect of the drug product with the exception of the observed vasculitis.

The combined embryofetal and pre-and post-natal development study with belimumab is described in the labeling section of this review.

**Recommendation:** There are no nonclinical safety concerns for administration of belimumab by the subcutaneous route.

The reviewer recommends approval of this BLA from the nonclinical perspective. Labeling should be modified as shown below or Section 1.3.3.
**Labeling Review:**
For this submission, the Sponsor provided a label for BENLYSTA identical to that approved for BENLYSTA by DPARP on January 2017. Specifically, the label incorporates information in compliance with the Pregnancy and Lactation Labeling Rule (PLLDR). A Pharmacological and Toxicological Review of BLA 125370 (dated August 18, 2016) reviewed the Sponsor's revised labeling for Sections 8.1, 8.2, and 13.1 of BENLYSTA® (belimumab) to comply with the Pregnancy and Lactation Labeling Rule.

Recommended labeling for Highlights of Prescribing Information, Sections 8.1 (Pregnancy), 8.2 (Lactation), and 13 (Nonclinical Toxicology) in the proposed product label are shown below.

**INDICATIONS AND USAGE in the HIGHLIGHTS OF PRESCRIBING INFORMATION**
BENLYSTA, a B-lymphocyte stimulator (BLyS)-specific inhibitor, indicated for:

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

*Pregnancy Exposure Registry*
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BENLYSTA during pregnancy. Healthcare professionals are encouraged to register patients by calling 1-877-681-6296.

*Risk Summary*
Limited data on use of belimumab in pregnant women, from observational studies, published case reports, and postmarketing surveillance, are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with SLE [see Clinical Considerations]. Monoclonal antibodies, such as belimumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero-exposed infant [see Clinical Considerations]. In an animal combined embryo-fetal and pre- and post-natal development study with monkeys that received belimumab by intravenous administration, there was no evidence of embryotoxicity or fetal malformations with exposures approximately 20 times the exposure at the maximum recommended human dose (MRHD). Belimumab-related findings in monkey fetuses and/or infants included reductions of B-cell counts, reductions in the density of lymphoid tissue B-lymphocytes in the spleen and lymph nodes, and altered IgG and IgM titers. The no-adverse-effect-level (NOAEL) was not identified for these findings; however, they were reversible within 3 to 12 months after the drug was discontinued [see Data]. Based on animal data and the mechanism of action of belimumab, the immune system in infants of treated mothers may be adversely affected. It is unknown, based on available data whether immune effects, if identified, are reversible [see Clinical Pharmacology (12.1)].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or
other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk:
Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, spontaneous abortion, and intrauterine growth restriction. Maternal lupus nephritis increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal anti-phospholipid antibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

Fetal/Neonatal Adverse Reactions:
Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to BENLYSTA™ in utero. Monitor an infant of a treated mother for B-cell reduction and other immune dysfunction [see Warnings and Precautions (5.5)].

Data

Animal Data:
In a combined embryo-fetal and pre- and post-natal development study, pregnant cynomolgus monkeys received belimumab at intravenous doses of 0, 5, or 150 mg/kg every 2 weeks from confirmation of pregnancy at Gestation Days (GD) 20 to 22, throughout the period of organogenesis (up to approximately GD 50), and continuing to either the day of scheduled cesarean section (GD 150 [late third trimester]) or the day of parturition. There was no evidence of maternal toxicity, embryotoxicity, or teratogenicity at exposure approximately 20 times the exposure at the MRHD of 200 mg subcutaneously (on an AUC basis with maternal intravenous doses up to 150 mg/kg). Belimumab-related findings in mothers included reductions of immature and mature B-cell counts and in fetuses and/or infants included reductions of immature and mature B-cell counts, reductions in the density of lymphoid tissue B-lymphocytes in the spleen and lymph nodes, reduced spleen weights, increased IgG titers, and reduced IgM titers. B-cell counts in infant monkeys exposed to belimumab in utero recovered by 3 months of age and in mothers after 1 year. IgG and IgM levels in infant monkeys recovered by 6 months of age and the reductions in B-lymphocytes in the lymph nodes and spleen were reversed by 1 year of age. Belimumab crossed the placenta, as it was detected in fetal cord blood and amniotic fluid on GD 150.

8.2 Lactation

Risk Summary

No information is available on the presence of belimumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Belimumab was detected in the milk of cynomolgus monkeys; however, due to species-specific differences in lactation physiology, animal data may not predict drug levels in
human milk. Maternal IgG is known to be present in human milk. If belimumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to belimumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of BENLYSTA to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BENLYSTA, and any potential adverse effects on the breastfed child from BENLYSTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Following an assessment of benefit versus risk, if prevention of pregnancy is warranted, females of reproductive potential should use effective contraception during treatment and for at least 4 months after the final treatment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of belimumab.

Effects on male and female fertility have not been directly evaluated in animal studies.
Table 11. Exposure margin table (AUC basis) for subcutaneous administration of belimumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose mg/kg/Q2W (IV)</th>
<th>AUC µg*day/mL Week 17</th>
<th>Exposure margin Clinical dose of Belimumab (SC) (QW) AUC_{0,∞} = 726 µg<em>day/mL (AUC_{0,∞} = 1452 µg</em>day/mL, Q2W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monkey ePPND(^A)</td>
<td>150</td>
<td>26,944</td>
<td>19</td>
</tr>
</tbody>
</table>

\(^A\)Maternal, Fetal and Neonatal toxicity study of LymphoStat-B™ administered bi-weekly by intravenous (bolus) injection to pregnant cynomolgus monkeys, including a one year postnatal evaluation (Study No. 1721-95)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRETT R JONES
05/09/2017

TIMOTHY W ROBISON
05/09/2017
I concur