Risk Management Plan for Gan & Lee Insulin Lispro Injection (Bysumlog)

Risk Management Plan (RMP) version to be assessed as part of this application:

Invent name	Bysumlog
Active Ingredient	Insulin Lispro
RMP Version number	0.2
Data lock point for this RMP	30-Apr-2023
Date of final sign-off	See signature page
Rationale for submitting an updated RMP	The updated RMP (Version 0.2) has been prepared in response to comments received as part of the D120 assessment.
Summary of significant changes in this RMP	1.Updated the invented name to Bysumlog throughout the document. 2.Updated Part 1 Product Overview Section：Changed “no additional monitoring” to “require additional monitoring”. 3.Changed Pharmaceutics form(s) and strengths to be consistent with SmPC. 4.Updated the company address and phone number of ProductLife Group. 5. Minor editorial changes for clarification purposes.
Other RMP versions under evaluation	Not applicable.
Qualified Person for Pharmacovigilance (QPPV) name	Francesco Ventura On behalf of Applicant / Marketing Authorisation Holder: Gan & Lee Pharmaceuticals Europe GmbH
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder Gan & Lee Pharmaceuticals’ QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
DKA	Diabetic Ketoacidosis
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GL Insulin Lispro Injection	Gan & Lee Insulin Lispro Injection
HbA1c	Glycated haemoglobin
MAH	Marketing Authorisation Holder
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package Leaflet
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SC	Subcutaneous
SD	Sprague-Dawley
SmPC	Summary of Product Characteristics
SS	Safety data set
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse events
TK	Toxicokinetic
US	United States

PART I: PRODUCT OVERVIEW

Table Part I.1 Product Overview

Active substance(s) (International non- proprietary name (INN) or common name)	Insulin Lispro
Pharmacotherapeutic group(s) (ATC Code)	Drugs used in diabetes. Insulins and analogues for injection, fast-acting (A10AB04)
Marketing Authorisation	Applicant: Gan & Lee Pharmaceuticals Europe GmBH Prinzenallee 11a, 40549 Düsseldorf, Germany
Medicinal product to which this RMP refers	**Bysumlog 100 units/ml solution for injection in pre-filled pen** Each pre-filled pen contains 300 units of insulin lispro in 3 ml solution. One ml contains 100 units of insulin lispro.
Invented name(s)	BYSUMLOG
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Insulin lispro is an Insulin Analog. The chemical classification of insulin lispro is Insulin. Molecular formula: $C_{257}H_{383}N_{65}O_{77}S_6$
	Summary of mode of action: Insulin lispro is homologous to human insulin with the exception of the penultimate lysine and proline residues which are reversed. The primary activity of insulin lispro is the regulation of glucose metabolism. In addition, insulins have several anabolic and anti-catabolic actions on a variety of different tissues. Within muscle tissue, this includes increasing glycogen, fatty acid, glycerol and protein synthesis and amino acid uptake, while decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.
	Important information about its composition: Gan & Lee Insulin Lispro Injection is a clear and colourless, sterile solution presented in a 3 mL cartridge that is assembled into a prefilled pen for use. Each millilitre contains the active ingredient, insulin lispro 100 units which is produced in *E.coli* by recombinant deoxyribonucleic acid (DNA) technology plus glycerol, zinc oxide, anhydrous disodium hydrogen phosphate, metacresol and water for injection. Sodium hydroxide or hydrochloric acid may have been used to adjust the acidity.
Hyperlink to the Product Information	Link to the latest approved (Applicant's country specific and Humalog Summary of Product Characteristics (SmPC)). EU Humalog Product Information:

	https://www.ema.europa.eu/en/medicines/human/EPAR/humalog#product-information-section Gan & Lee Insulin Lispro Injection Product Information: Section 1.3.1 SmPC, Labelling and Package Leaflet
Indication(s)	Current: For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Insulin Lispro is also indicated for the initial stabilisation of diabetes mellitus.
	Proposed: Not applicable.
Dosage	Current: Insulin Lispro may be given shortly before meals. When necessary, Insulin Lispro can be given soon after meals. The insulin lispro 100 units/ml pre-filled pen delivers 1 – 60 units in steps of 1 unit in a single injection. The number of insulin units is shown in the dose window of the pen regardless of strength and no dose conversion should be done when transferring a patient to a new strength or to a pen with a different dose step. Insulin Lispro can be used in conjunction with a longer-acting insulin or oral sulphonylurea agents, on the advice of a physician. *Method of administration:* Insulin Lispro preparations should be given by subcutaneous (SC) injection. Subcutaneous administration should be in the upper arms, thighs, buttocks, or abdomen. Use of injection sites should be rotated so that the same site is not used more than approximately once a month, in order to reduce the risk of lipodystrophy and cutaneous amyloidosis. When administered SC care should be taken when injecting insulin lispro to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use the proper injection techniques.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: 3 ml (100 units/ml) sterile clear and colourless solution for SC injection in pre-filled pen.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring?	Yes

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Gan & Lee (GL) Insulin Lispro Injection, hereafter referred to as Bysumlog, is a sterile, clear, colorless solution for subcutaneous injection indicated to improve glycaemic control in adults and paediatric subjects with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM).

Diabetes is a chronic, progressive disease that, if inadequately treated, can lead to significant morbidity, including macrovascular and microvascular complications, and significantly increased mortality. In conjunction with ongoing patient lifestyle education regarding self-management of the disease, SC insulin is the mainstay of treatment for patients with T1DM and may be used to treat patients with T2DM.

Type 1 Diabetes Mellitus characterised by autoimmune beta (β)-cell destruction, usually leading to absolute insulin deficiency, and T2DM (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance), are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Children with T1DM, the most common form of diabetes in the paediatric population, typically present with symptoms of polyuria/polydipsia, and approximately one-third present with diabetic ketoacidosis (DKA) (ADA, 2020). Occasionally patients with T2DM may present with DKA.

Diabetes is diagnosed based on plasma glucose criteria, either the fasting plasma glucose value or the 2-h plasma glucose value during a 75-g oral glucose tolerance test, or Glycated haemoglobin (A1c) criteria (ADA 2020).

The epidemiology, pathophysiology, developmental considerations, and response to therapy in paediatric-onset diabetes are different from adult diabetes. There are also differences in recommended care for children and adolescents with T1DM as opposed to T2DM.

In T1DM, consideration must be given to changes in insulin sensitivity related to physical growth and sexual maturation, the ability to provide self-care, supervision in the childcare and school environment, neurological vulnerability to hypoglycaemia and hyperglycaemia in young children, and possible adverse neurocognitive effects of DKA. In T2DM, lifestyle modifications, self-management of diabetes and pharmacological medications play a pivotal role in its management.

Incidence and Prevalence:

From a global perspective, an estimated 26.9 million people of all ages equal to 8.2% of the U.S. population had diagnosed diabetes in 2018 (Available from: https://www.cdc.gov/diabetes/data/statistics-report/index.html). This total included 210,000 children and adolescents younger than 20 years of age, and of these approximately 187,000 had T1DM. During 2014-2015, the estimated annual number of newly diagnosed cases in the United

States included 18,291 children and adolescents younger than 20 years of age with TIDM and 5,758 children and adolescents aged 10 to 19 years with T2DM.

In Europe according to a metanalysis, the incidence of T1DM is 15 per 100,000 population, and the prevalence of T1DM is 12.2 per 10,000 people (Mobasseri *et al*, 2020).

The global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014. An estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980 (Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes). The causes are complex, but the rise is due in part to increases in the number of people who are overweight, including an increase in obesity and a widespread lack of physical activity. This reflects an increase in associated risk factors such as being overweight or obese.

The main existing treatment options

Diabetes of all types can lead to complications in many parts of the body and increase the risk of dying prematurely. It has been shown that a proportion of diabetes and its complications can be prevented by a healthy diet, regular physical activity, maintaining normal body weight and avoiding tobacco use.

Standard of care includes lifestyle management, nutrition, pharmacologic approach (human insulin, insulin analogues, oral hypoglycaemic agents, glucagon-like peptide receptor agonist or bariatric surgery.

Important co-morbidities

According to a World Health Organisation report, when diabetes is not treated or well managed, complications are life threatening. Acute complications contribute to mortality, costs and poor quality of life. People with diabetes are at greater risk of developing conditions such as cardiovascular disorders, neurological (nervous system) disorders, diabetic eye disease and kidney disease. Severe hyperglycemia may be life-threatening if it triggers DKA in T1DM and T2DM, and hyperosmolar coma in T2DM. Severe hypoglycemia may result in seizures or loss of consciousness.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Chronic diabetes can damage the heart, blood vessels, eyes, kidneys and nerves, and increase the risk of heart disease and stroke. The result can be reduced blood flow, which if combined with neuropathy in the feet increases the chance of foot ulcers, infection and the eventual need for limb amputation. Diabetic retinopathy is an important cause of blindness and occurs as a result of long- term accumulated damage to the small blood vessels in the retina.

Diabetes is one of the leading causes of kidney failure. Uncontrolled diabetes in pregnancy can have a devastating effect on both mother and foetus, substantially increasing the risk of fetal loss,

congenital malformations, stillbirth, perinatal death, obstetric complications, and maternal morbidity and mortality. Gestational diabetes increases the risk of some adverse outcomes for mother and offspring during pregnancy, childbirth and immediately after delivery such as high blood pressure resulting in seizures during pregnancy. However, it is unknown what proportion of obstructed births or maternal and perinatal deaths can be attributed to hyperglycaemia. Due to increased life span, diabetes over long term has also been associated with increased rates of specific cancers and increased rates of physical and cognitive disability (Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes).

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

The non-clinical development of Bysumlog primarily relied on the data submitted in Humalog insulin Lispro NDA 020563 and EMEA/H/C/000088 Marketing Authorisation Application (MAA) and followed the FDA and EMA guidelines for developing biosimilar products. Therefore, a full non-clinical development programme was not required. Only those studies that were required to support a biosimilar product application and to ascertain the safety of the product were conducted.

In vitro pharmacology studies were conducted to compare structural and biological properties of Bysumlog and Humalog (US and EU). All data supported the conclusion that Bysumlog was highly similar to the reference standard and reference listed drug Humalog with respect to physicochemical properties and biological function.

In vitro receptor binding assay, receptor autophosphorylation assay, and three metabolic activity assays (glucose uptake, lipogenesis, and glycogen formation) demonstrated that Bysumlog is biologically comparable to Humalog in terms of binding affinity for insulin receptor (IR)-A and IR-B, inducing receptor autophosphorylation and insulin-like growth factor-1 receptor (IGF-1R) autophosphorylation, as well as stimulating metabolic activities.

Toxicity

No formal acute toxicity studies have been conducted. However, the toxicity after a single dose can be assessed from the repeated-dose SC toxicity studies in Sprague-Dawley (SD) rats (doses from 10 U/kg/day and 50 U/kg/day).

A 28-day repeated dose toxicity study (S14049) with a separate cohort for toxicokinetic (TK) analysis to evaluate the potential toxicity, TK characteristics and immunogenicity of Bysumlog in comparison with Humalog were conducted in SD rats (study report S1409). The selection of rats for this study was based on the animal used for Humalog repeat-dose toxicity studies.

The repeat dose toxicity study showed 3 unscheduled deaths (1 male rat at 50 U/kg Humalog (US) and 2 male rats at 50 U/kg Humalog (EU)). No abnormal gross necropsy findings were observed; these mortalities were considered due to severe hypoglycemia. No gender differences in the systemic exposure to insulin and no apparent differences after 4 weeks of once-daily SC administration of either Bysumlog or Humalog at doses up to 50 U/kg.

A comparable number of main and recovery animals developed serum anti-drug antibodies after treatment with Bysumlog and Humalog (US and EU), anti-drug antibodies occurrence is not expected to impact TK and toxicity when compared to Humalog (US and EU) and Bysumlog-treated groups.

Local tolerance was assessed as part of the SC repeated-dose studies in SD rats. Mild local irritation in the form of red brown discoloration at the injection site (dosing area) was observed during the necropsy. As this was found in animals from all groups except for the Group 1

controls, and the incidence was very low (no more than 2 animals in any group), this was likely a mild local reaction to test article injection, and not toxicologically important.

Overall, the toxicological profile of Bysumlog and Humalog (US-approved and EU-licensed) were comparable.

Safety pharmacology

Stand-alone studies evaluating the safety pharmacology of Bysumlog were not conducted due to the absence of safety-related findings in the repeat dose toxicity studies.

Other toxicity-related information or data

Gan & Lee did not conduct additional studies beyond the available data for Humalog Insulin Lispro Injection for the development of Bysumlog as such studies are not in the scope of a biosimilar development program in accordance with FDA Guidance for Industry or Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015), EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) and EMA Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1).

Conclusion

There were no new key safety findings from non-clinical studies that would preclude the use of Bysumlog in humans. The non-clinical profile is considered comparable between Bysumlog and Humalog (EU and US).

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Cumulative Subject Exposure in Clinical Trials

Clinical Studies Overview

A number of clinical studies (one Phase 1, one Phase 2, two Phase 3 and one post-marketing study) of Bysumlog were conducted in order to establish biosimilarity and safety versus Humalog. There are no ongoing studies.

Study GL-LSP-1006: This was a Phase 1 study, a glucose clamp trial investigating the biosimilarity of Bysumlog with both EU-approved and US-licensed Humalog® in healthy male subjects. The primary objective was to evaluate PK and PD equivalence of Bysumlog to US Humalog and to EU Humalog. The secondary objectives were to compare the PK and PD parameters of the three investigational medicinal products and to evaluate safety and local tolerability. In total, 38 subjects were included in the trial and randomized to one of the treatment sequences. Thirty-six of the 38 randomized subjects completed the whole trial period. Two subjects discontinued prematurely, both after the first dosing visit with US Humalog and both on own initiative. The study demonstrated, both PK and PD similarities of Bysumlog to US Humalog and to EU Humalog. Bysumlog was safe and well-tolerated with no serious AEs or injection site reactions. Safety and tolerability were good for Bysumlog, US Humalog and EU Humalog, with no serious AEs, mostly mild-grade AEs. There were no clinically significant findings or changes in safety laboratory results, vital signs, ECGs, and physical examination results.

Study Lispro 2012 Gan Lee: This was a Phase 2 open-label comparative randomized double-crossover multicentre clinical study was conducted to compare efficacy and safety of Bysumlog and Humalog in subjects with T1DM and T2DM. A total of 72 subjects, aged 18 to 65 years with type 1 or type 2 diabetes requiring insulin participated in the trial. Of the total 72 subjects, 71 completed the study and 1 opted for voluntary withdrawal from study. Subjects were randomised into two groups (1-Lispro-Humalog; 2-Humalog-Lispro).

The safety data set (SS) was defined as the full analysis set except subjects who never received treatment. The SS was the primary data set for the safety evaluation. All 72 subjects were included in the SS set, (36 subjects each for sequences Lispro-Humalog and Humalog-Lispro). There were no deaths or SAEs reported during the study. At least one AE was reported by 12/72 (16.7%) subjects of the main group, and by 16/72 (22.22%) subjects in the control group. Hypoglycaemia was the most common AE seen across groups. In the Bysumlog group, hypoglycaemia was observed in 11 (15.3%) subjects (25 cases), and in the control group in 12 (16.7%) subjects (31 cases). Furthermore, increased alanine aminotransferase, aspartate aminotransferase, bilirubin, atony and dizziness were also reported in the absence of significant difference between groups.

During the study no significant increase in the insulin antibodies level was noted neither in the Lispro group, nor in the Humalog group.

Study results indicated that the efficacy of the test medicinal product Bysumlog is comparable in efficacy to the medicinal product Humalog when administered to subjects with T1DM and T2DM. Safety data suggest that safety and tolerability of Lispro is comparable to that of Humalog.

Study 2003L02125 (BJDB002R): This was a Phase 3 randomised, open-label, parallel, multicentre comparison study conducted to evaluate the efficacy and safety of Bysumlog and Humalog in patients with T1DM and T2DM after 12 weeks of treatment. A total of 482 subjects aged between 18 to 75 years were screened. Although 20 subjects dropped out of the study for various reasons (10 subjects experienced AEs, 3 subjects for no visit, 2 subjects for protocol violation, 2 subjects for unknown reason and 2 subjects for other reasons, 1 subject had no or no enough efficacy), all subjects were included in the full safety and efficacy analysis with 361 subjects in the Lispro group (T1DM - 49; T2DM - 312) and 121 subjects in the Humalog group (T1DM; 16; T2DM; 105).

The study results indicated that both Bysumlog and Humalog enabled subjects with type 1 or type 2 diabetes to achieve good glycaemic control. Using HbA1c, fasting blood glucose, and 2-hr postprandial venous blood glucose levels as bioequivalence criteria, Bysumlog had similar therapeutic effects to Humalog in diabetic subjects.

In 482 randomised controlled subjects, a total of 123 AEs were reported in 100 subjects after treatment. The incidence rate for AEs considered related to study drug was 5% and 3.3% for Bysumlog and Humalog respectively. There was no statistical significance between the two groups. A total of 5 subjects in the two groups reported 7 SAEs, excluding hypoglycaemia during the study, none of which were related to the investigational drugs. There was one death reported with unknown reason in the Bysumlog group.

Overall, Bysumlog showed equivalent safety, efficacy, good tolerability and compliance to Humalog.

Study ID KI/0513-2

An open-label, Phase 3, comparative, randomised, multicentre clinical study to evaluate the efficacy, safety and immunogenicity of the Bysumlog was conducted in Russia. The study enrolled 118 subjects with 59 subjects in the study group Bysumlog and 59 subjects in the group with reference drug, Humalog. Safety and immunogenicity assessments were conducted for 118 subjects. Overall, the subjects demonstrated no less efficacy and safety of Bysumlog and Humalog.

Immunogenicity assessment: Taking into account the immunogenicity assessment at 3 different points, the study concluded that the immunogenicity profiles for the investigational drug and reference drug were the same.

Exposure During Clinical Trials

Up to 30-Apr-2023, 4 clinical studies were completed with Insulin Lispro. The estimated cumulative treatment subject exposure is provided in Table SIII. 1. The cumulative subject exposure from completed clinical studies of the demographic data is presented by age and gender inTable SIII. 2.The total in Table SIII. 1 is greater than the total in Table SIII. 2. This is because Table SIII. 1presents unique counts of subjects per treatment arm. If a subject is exposed to more than 1 treatment including placebo or comparator, the subject is counted for each treatment. In exposure by subgroup table (Table SIII. 2), a subject is counted only once, and, hence, the total number of subjects in cumulative exposure may be higher than the total number of subjects in subgroup tables.

Table SIII. 1 Estimated cumulative treatment subject exposure in all clinical studies, full analysis set

Treatment	Number of subjects	Study Reference
Bysumlog	36^ 35* 361 59	GL-LSP-1006 Lispro 2012-GL 2003L02125 KI/0513-2
EU Humalog	36^ 36 121 59	GL-LSP-1006 Lispro 2012-GL 2003L02125 KI/0513-2
US Humalog	38^	GL-LSP-1006
Total	**781**	

*In study Lispro 2012-GL, a total of 36 subjects were randomised to GL Insulin Lispro group, however one subject dropped off the study pre-maturely.

^In study GL-LSP-1006, a total of 38 subjects were recruited for the study, however 2 subjects dropped out prematurely post exposure to US Humalog. The 36 subjects randomised in this trial were exposed to all three insulins (GL Insulin Lispro, EU Humalog and US Humalog) with wash out period of 3-14days. These 36 subjects were exposed to three different treatments.

In the following table (Table SIII. 2), details of age group and gender of the subjects involved in all 4 completed clinical studies are provided.

Table SIII. 2 Age group and gender of subjects involved in all 4 clinical studies (GL-LSP-1006, Lispro 2012-GL, 2003L02125, and KI/0513-2)

Age group	Subjects		
	Male	Female	Total
<18	0	0	0
18 – 75	336	371	707
>75	0	0	0

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Reason for exclusion: Biosimilar development requires only the most sensitive and responsive subjects for study.

Considered to be included as missing information: No

It is not considered that the subject populations excluded from study in the clinical trials presents a limitation in relation to predicting the safety of the medicinal product in real life use.

SIV.2 Limitations to detect adverse reactions in clinical trial development programme

The clinical development programme is unlikely to detect certain types of AEs such as adverse reaction (AR)s with a long latency, or those caused by prolonged or cumulative exposure as the programme was designed only to ascertain the equivalence of Bysumlog to the Reference Product.

In addition, the clinical development programme was intended to determine if there were any differences in safety profile between reference and comparator products such as immunogenicity, hypoglycaemia or SAEs as well as serving to identify of any Suspected Unexpected Serious Adverse Reactions or new safety signals, or differences in efficacy.

For biosimilar medicinal products it is not required by the EMA or FDA to re-establish the benefits of the reference product, in this case insulin lispro. Therefore, not all patient populations were studied but only those that constitute the most sensitive and homogeneous group that provide the best opportunity to detect any differences between the biosimilar candidate and the originator medicine. It is not considered that any of the patient populations not studied in the clinical development programme constitutes missing information.

SIV.3 Limitations in respect to populations typically under-represented in clinical development programme

Table SIV.1 Populations not studied in clinical trials

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Subjects with relevant comorbidities Subjects with hepatic impairment Subjects with renal impairment Subjects with cardiovascular impairment Immunocompromised subjects Subjects with a disease severity different from inclusion criteria in clinical trials	
Population with relevant different ethnic origin	
Subpopulations carrying relevant genetic polymorphisms	
Paediatrics	

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Cumulative and Interval Patient Exposure from Marketing Experience

Bysumlog is intended for use by diabetic patients, with the dosage and regimen individually adjusted by the health care provider depending on type (T1DM or T2DM), severity, weight, and age.

SV.1.1 Method used to calculate exposure (Patient Exposure)

An estimation was made on patient exposure to Bysumlog marketed from 2007 to 30 Apr 2023.

An estimate of patient exposure was calculated based on total sales in international units by multiplying counting units for each injectable formulation with the strength in U/mL. Total sales in Units were divided by WHO defined daily dose (DDD) for insulin lispro and 365 to estimate patient-years.

$$\text{Patient exposure (patient-years)} = \frac{\text{Total sales in Units}}{\text{DDD} * 365}$$

The WHO DDD for insulin lispro is 40 units.

SV.1.2 Exposure

GL Insulin lispro was first approved in China and began marketing in 2007. The cumulative exposure to insulin lispro (100 U/mL) could be estimated to be [redacted] patient-years.

PART II: MODULE SVI - ADDITIONAL REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

It is not expected the Bysumlog has the potential for misuse for illegal purposes.

Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure. Hypoglycaemia may be associated with listlessness, confusion, palpitations, headache, sweating and vomiting.

Mild episodes of hypoglycaemia can usually be treated with oral administration of glucose or other sugar or saccharated products.

Correction of moderately severe hypoglycaemia can be accomplished by intramuscular (IM) or SC administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously. If the patient is comatose, glucagon should be administered via IM or SC route.

Sustained carbohydrate intake and observation may be necessary to prevent recurrence.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

The comparability protocols demonstrated biosimilarity of Bysumlog to reference product Humalog by means of physicochemical analyses, structural and impurity profile comparisons and biological analyses. The comparability exercise demonstrated the biosimilarity of Bysumlog to the reference product by means of physicochemical analyses, structural and impurity profile comparisons and biological analyses. This has been confirmed in non-clinical and clinical studies which indicate that Bysumlog has a similar safety profile to the reference biological medicinal product. Data from clinical trials conducted by G&L were taken into account when determining the safety specification for this biosimilar product.

With respect to safety for a biosimilar, the main focus lies on the immunogenicity of the new product compared to the reference product. No increased risk for development of anti-insulin lispro antibodies of Bysumlog compared with Humalog has been identified, indicating similarity in term of immunogenicity risk (confirmed by both a comparability exercise and a Phase 2 study which included an assessment of immunogenicity [Study LISPRO 2012 GL]). In addition, no relevant differences were observed between treatment groups with regards to treatment emergent adverse events (TEAEs) involving hypoglycaemia across clinical studies performed by the applicant where this was assessed.

G&L considers Bysumlog to be biosimilar to EU and US-sourced reference product, Humalog.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

There are no risks considered important for inclusion in the list of safety concerns for the RMP as no new important identified or important potential risks associated with Bysumlog have been identified when compared with the reference product.

Risk-benefit impact:

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

There are no identified or potential risks that are considered to be “important”.

SVII.3.2. Presentation of the missing information

There is no information considered to be “missing information”.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The MAH is committed to monitoring of all safety concerns during the post marketing phase and to collect and analyse Individual Case Safety Report in order to detect signals and better qualify all potential safety concerns and missing information.

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are proposed.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned post-authorisation efficacy studies.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Bysumlog (insulin lispro)

This is a summary of the Risk Management Plan for Bysumlog. The RMP details important risks of Bysumlog, how these risks can be minimised, and how more information will be obtained about the Bysumlog's risks and uncertainties (missing information).

Bysumlog's SmPC and Package Leaflet (PL) give essential information to healthcare professionals and patients on how Bysumlog should be used.

Important new concerns or changes to the current ones will be included in updates of GL Insulin Lispro RMP.

I. The medicine and what it is used for

Bysumlog is suitable for diabetics who need insulin to maintain normal blood sugar homeostasis. Bysumlog contains insulin lispro as the active substance and is given by SC route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Bysumlog, together with measures to minimise such risks and the proposed studies for learning more about Bysumlog's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can include the following:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL, and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine *risk minimisation measures*.

In addition to these measures, information about ARs is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Bysumlog are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Bysumlog. Potential risks are concerns for

which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Bysumlog.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Bysumlog.

PART VII: ANNEXES

Table of Contents of Annexes

ANNEX 4 - SPECIFIC ADR FOLLOW-UP FORMS

Not applicable.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Not applicable.

ANNEX 7 - OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

- American Diabetes Association (ADA) 2020, 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020, *Diabetes Care* 2020 Jan; 43(Supplement 1): S14-S31. [Available at: https://doi.org/10.2337/dc20-S002].
- Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed [10 Mar 2023].
- Global report on diabetes [Internet]. World Health Organization. World Health Organization; [cited 16 Mar 2023]. Available from: https://www.who.int/publications/i/item/9789241565257.
- Mobasseri M et al, Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis., *Health Promot Perspect*. 2020; 10(2): 98–115.
- World Health Day 2016: Beat diabetes [Internet]. World Health Organization; [cited 10 Mar 2023]. Available from: https://www.who.int/news-room/events/detail/2016/04/07/default-calendar/world-health-day-2016#:~:text=WHO%20projects%20that%20diabetes%20will,use%20the%20insulin%20it%20produces.