26 February 2026
EMA/62211/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bysumlog

International non-proprietary name: Insulin lispro

Procedure No. EMEA/H/C/006158/0000

Note

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
ADA	Anti-Drug Antibody
AE	Adverse Event
AET	Antimicrobial Effectiveness Testing
ANOVA	Analysis of variance
$AUC_{GIR,0\text{-}12\ h}$	Area under the GIR curve from 0 to 12 hours
$AUC_{GIR.0\text{-}2h}$	Area under the glucose infusion rate curve from 0 to 2 hours
$AUC_{GIR.0\text{-}4h}$	Area under the glucose infusion rate curve from 0 to 4 hours
$AUC_{GIR.0\text{-}6h}$	Area under the glucose infusion rate curve from 0 to 6 hours
$AUC_{GIR.6\text{-}12h}$	Area under the glucose infusion rate curve from 6 to 12 hours
$AUC_{ins.0\text{-}2h}$	Area under the insulin lispro concentration curve from 0 to 2 hours
$AUC_{ins.0\text{-}4h}$	Area under the insulin lispro concentration curve from 0 to 4 hours
$AUC_{ins.0\text{-}6h}$	Area under the insulin lispro concentration curve from 0 to 6 hours
$AUC_{ins.0\text{-}inf}$	Area under the insulin lispro concentration curve from 0 hours to infinity
$AUC_{ins.6\text{-}12h}$	Area under the insulin lispro concentration curve from 6 to 12 hours
AUC_{last}	Area Under the Concentration-Time Curve
BET	bacterial endotoxin test
BW	Body Weight
CCIT	closure integrity test
CCS	Container closure system
CEX-HPLC	Cation-Exchange High-Performance Liquid Chromatography
CHO	Chinese Hamster Ovary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
$C_{ins.max}$	Maximum observed insulin lispro concentration within 12 hours post dose
CIPC	Critical In-process Control
CMC	Chemistry, manufacturing, and controls
C_{max}	Maximum observed plasma concentration
CoA	Certificate of Analysis
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CSR	Clinical study report
DP	Drug Product
DNA	Deoxyribonucleic acid
DSP	Downstream process

DOES	Design of experiments
ECL	Electrochemiluminescence
EMA	European Medicines Agency
EU Humalog	EU-authorized Humalog
FDA	Food and Drug Administration
GCP	Good clinical practice
Geometric LS-mean	LS-mean based on log-transformed data
GIR	Glucose infusion rate
GIR_{max}	Maximum observed glucose infusion rate within 12 hours post dose
GL	Gan and Lee Pharmaceuticals
GL insulin lispro	Gan & Lee insulin lispro injection
GLP	Good Laboratory Practices
HF	Human factor
HMWP	High Molecular Weight Protein
I	Impact
ICH	International Council for Harmonisation
IFU	Instructions for use
IGF-1R	Insulin-Like Growth Factor-1 Receptor
(C)IPC	(critical) in-process control
IPM	in-process monitoring
IR-A	Insulin Receptor A
IR-B	Insulin Receptor B
ISI	Integrated Summary of Immunogenicity
KPP	key process parameters
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LLOQ	Lower limit of quantification
LS	Least Squares
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MCB	Master Cell Bank
MO	Major Objection
MSIA-LC-MS/MS	Mass Spectrometric Immunoassay coupled with Liquid Chromatography–Tandem Mass Spectrometry
ml	Millilitre
N/A	Not applicable
NaOH	Sodium hydroxide
NEP	Non-endotoxin pyrogen
NKPP	Non-key process parameter
NOAEL	No observable adverse effect level
NOR	Normal operating range

PD	Pharmacodynamics
pH	Potential hydrogen
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/pharmacodynamics
PPQ	Process Performance Qualification
PPS	Per protocol set
QA	Quality attributes
QR	Quality Range
RP-HPLC	Reversed-phase high-performance liquid chromatography
QTPP	Quality Target Product Profile
RMP	Risk management plan
PDE	Permitted daily exposure
SA	Scientific Advice
SC	Subcutaneous
SD	Standard deviation
SD rat	Sprague Dawley rat
SPR	Surface Plasmon Resonance
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
$t_{GIR.max}$	Time to maximum glucose infusion rate
TK	Toxicokinetic
US	United States of America
US Humalog	US- authorized Humalog
USP	Upstream process
USP	United States Pharmacopeia
URRA	Use Related Risk Assessment
WCB	Working Cell Bank
WRS	Working reference standard
α	Alpha
β	Beta

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gan & Lee Pharmaceuticals Europe GmbH submitted on 17 August 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Bysumlog, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Bysumlog is also indicated for the initial stabilisation of diabetes mellitus.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Humalog, 100 units/ml, solution for injection in pre-filled pen
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 30/04/1996
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/96/007

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Humalog, 100 units/ml, solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 30-04-1996
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/96/007

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Humalog, 100 units/ml, solution for injection
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 30-04-1996
- Marketing authorisation granted by:

- Union
- (Union) Marketing authorisation number(s): EU/1/96/007/031, EU/1/96/007/032

- Bioavailability study number(s): GL-LSP-1006

1.3. Information on Paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
26 April 2018	EMEA/H/SA/3774/1/2018/III	Armin Koch, Kolbeinn Gudmundsson
10 November 2022	EMA/SA/000100386	Juha Kolehmainen, Elina Rönnemaa

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Quality: overall adequacy of the proposed comparative analytical similarity programme; evaluation of analytical biosimilarity, namely the approach to define the multipliers for quality range assessment; quality attributes to be included in the comparative analytical assessment; batch selection approach in the comparative analytical assessment; zinc content and thermal stability.
- Non-clinical: adequacy of the non-clinical data provided.
- Clinical: design of the pivotal phase 1 PK/PD study and design aspects of the planned phase 3 study, including inclusion and exclusion criteria, non-study insulin treatment, study duration and blinding; summative human factors study containing simulated use and differentiation to various marketed pens and bridging study to demonstrate comparability between the existing UnoPen and a newly developed disposable pen.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Thalia Marie Estrup Blicher

The application was received by the EMA on	17 August 2023
The procedure started on	28 September 2023

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 December 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	09 October 2025
The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection at one manufacturing site in China between 13-15 and 18-19 March 2024. The outcome of the inspection carried out was issued on	28 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 January 2026
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 February2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Bysumlog on	26 February 2026
The CHMP adopted a report on similarity of Bysumlog with Amglidia on (see Appendix on similarity)	26 February 2026

2. Scientific discussion

2.1. About the product

Bysumlog (insulin lispro) was developed as a proposed biosimilar to the Eli Lilly Humalog (insulin lispro injection) for subcutaneous (SC) injection, hereafter referred to as Humalog.

It is noteworthy that the Risk Management Plan (RMP) includes the information that GL Insulin Lispro was first approved in China and has been marketed already in 2007. The cumulative exposure to insulin lispro (100 U/mL) is estimated by the Applicant to be 88,027 patient-years. (See also sections 2.3 and 3.3 of this AR.)

The claimed therapeutic indications are the same as the therapeutic indications of Humalog:

For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Bysumlog is also indicated for the initial stabilisation of diabetes mellitus.

2.2. Type of Application and aspects on development

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) provided advice to the Applicant in a pre-submission meeting and through a scientific advice (SA) path on two occasions:

- EMA initial scientific advice letter 26 April 2018
- EMA initial scientific advice letter 10 November 2022
- EMA Pre-MAA Meeting Preliminary Comments 23 Jan 2023

The initial scientific advice on quality pertained to proposed comparative analytical similarity program for Bysumlog, comparing the Gan & Lee Drug Product (DP) to the insulin lispro reference medicinal product Humalog. More specifically, advice was given on establishment of QTPP, suitable reference medicinal product, predefining similarity criteria and analytical techniques.

The follow-up Scientific Advice pertained to visible particles, zinc content and thermal stability, as well as issues concerning analytical biosimilarity assessment such as approach to defining quality range, quality attributes to be included and batch selection approach.

In the pre-Marketing Authorisation Application (pre-MAA) meeting, the approach for choosing batches for batch analysis, stability, justification of specifications, and comparative analytical assessment, as well as pyrogen test, were discussed. The Applicant followed scientific advice and recommendations provided by the CHMP and during the pre-MAA meeting. Several recommendations given for the analytical similarity assessment were followed. Bacterial endotoxin test was used instead of rabbit pyrogen test.

Regarding the non-clinical data, at the time of Scientific Advice (SA), some of the *in vitro* activity analyses were not yet conducted but were planned. The overall test battery plan was considered adequate.

The clinical development program includes one Phase I PK/PD similarity study, GL-LSP-1006, designed to demonstrate pharmacokinetic (PK) and pharmacodynamic (PD) equivalence of Bysumlog with both EU-approved Humalog and US-licensed Humalog (Reference Products) in healthy male subjects. In the SA in 2018, the CHMP agreed with the proposed PK/PD study highlighting some issues that have been respected in the execution of the study.

The CHMP also stated that immunogenicity should be evaluated as instructed in the guideline. For this purpose, the Applicant compiled an Integrated Summary of Immunogenicity (ISI).

In 2018, the Applicant was also planned a phase 3 trial in type 1 diabetic patients and received advice on their planned protocol. However, the planned phase 3 clinical study, GL-LSP1-3003, was ended before any patients were administered the study drug, in accordance with SA from the EMA and the FDA that no phase 3 trials are required for biosimilar insulins. The Applicant provided a comparative analysis of the proposed disposable pen consisting of Bysumlog integrated in a UnoPen and Humalog KwikPen. The Applicant stated that it was conducted in accordance with the FDA guidance for Industry, *'Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications'* (October 2018). The CHMP recommended during SA that a human factor (HF) study testing distinguishability of the planned pen from other common pen devices among pharmacists, nurses, paediatric and adult patients and caregivers was needed for patient safety. Three HF validation tests were performed by the applicant (see section 'User-related aspects of pen device').

Of note, the RMP includes information on 3 clinical studies completed with Bysumlog in addition to the currently reported clamp study GL-LSP-1006: one Phase 2 open-label comparative randomized double-crossover multicentre clinical study and two Phase 3 randomised, open-label, parallel, multicentre comparison studies. According to the RMP, there are no ongoing clinical trials. The estimated total cumulative treatment subject exposure in clinical trials is 781 subjects, and since 2007 the cumulative exposure is 88,027 patient-years. The Clinical Study Reports (CSRs) of the earlier trials were not included in the MAA, but the Applicant included short descriptions of these studies and their results in the RMP. The Applicant stated that Bysumlog showed equivalent safety, efficacy, good tolerability and compliance to Humalog and similar immunogenicity profile of Bysumlog and Humalog. As no clinical trials are required for a biosimilar insulin, it is considered acceptable that the CSRs of these studies were not included in the current MAA dossier.

2.3. Quality aspects

2.3.1. Introduction

The finished product (FP) is presented as solution for injection in pre-filled pen containing 100 units/ml of insulin lispro as active substance (AS). Each pre-filled pen contains 3 ml equivalent to 300 units of insulin lispro.

Other ingredients are: metacresol, glycerol, anhydrous disodium hydrogen phosphate, zinc oxide, water for injection, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

The product is available in type I borosilicate glass cartridges, sealed with bromobutyl disc seals and plunger heads and are secured with aluminium seals, The 3 ml cartridges are sealed in a disposable pen injector.

Packs of 1 and 5 pre-filled pens.

2.3.2. Active Substance

2.3.2.1. General Information

Insulin lispro (INN) is a human insulin analogue and consists of two chains. The A-chain is composed of 21 amino acids, and the B-chain is composed of 30 amino acids. Its primary structure is identical to that of human insulin except that position 28 and 29 in the B-chain are Lys and Pro, respectively, whereas this sequence is

reversed in human insulin. Insulin lispro is fast-acting insulin. The primary activity of insulin lispro is the regulation of glucose metabolism.

2.3.2.2. Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Insulin lispro AS is manufactured at Gan & Lee Pharmaceuticals (No. 8, Nanfeng West First Road, Beijing, China). Initially, a valid proof of EU-GMP compliance for this site was missing and a Major Objection was raised. During the procedure, a valid proof of EU-GMP compliance for the manufacturing site has been provided.

Gan & Lee insulin lispro is produced by recombinant DNA technology using *E. coli* K12 as host cell for the expression vector. A two-tiered cell bank system including the master cell bank (MCB) and several working cell banks (WCB) has been established and is adequately controlled to ensure a consistent production of insulin lispro. Appropriate safety precautions and controls concerning the absence of bacteria, mycoplasma, and viruses has been considered for chromatography resins, filtration membranes, media, and cell banks.

The active substance manufacturing process has been adequately described. The upstream process (USP) consist of: inoculation with WCB and seed culture expansion steps; fed-batch production fermentation; cell harvest, cell washing, and concentrate preparation. A limit is defined for the number of cell generations at the end the batch.

The downstream process includes denaturation of the inclusion body and continues through refolding, enzyme digestion, ultrafiltration/diafiltration (UF/DF) and chromatography steps, crystallization and freeze drying.

The final AS is a freeze-dried powder packaged into sterilized bottles. The description of the manufacturing process is provided in the form of a flow chart and sequential description of every manufacturing step. The classification of process parameters criticality (critical process parameters (CPP), (non)-key process parameters (KPP or NKPP)), ranges, and in-process controls (IPC) / in-process monitoring (IPM) have been presented.

The quality of the AS is ensured by controlling the CPPs for each of the steps. The output from each process step is monitored by in-process controls, which are adequately listed with their action limits/acceptance criteria. In addition, the microbial control in the process includes bioburden reduction filters at key steps and the establishment of maximum hold times for in-process intermediates. Overall, the identification and justification of critical quality attributes (CQAs), CPPs and IPCs, the acceptable range of CPPs and the acceptance criteria of IPC are adequately described, and the presented process parameters and controls seem appropriate.

A major objection was raised for the cell bank has been found and adequately addressed. The applicant has performed a risk assessment and an extensive design of experiment process characterisation studies to evaluate the process impact on product quality, as well as introduced an amended control strategy. The data is adequate.

Process validation

The ability of the manufacturing process to produce qualified products within the predefined acceptable range was verified in the process performance qualification (PPQ). Consecutive commercial scale batches were performed for PPQ. Prior to the start of the PPQ, the qualification of the facility, equipment and utilities was completed. Sampling during the PPQ followed a pre-defined test strategy and samples were tested with the

validated or qualified analytical methods. Process parameters and in-process control results were evaluated against the predefined ranges, acceptable criteria or limits. Overall, the AS process validation is considered well conducted and acceptable. The proposed process parameters and in-process controls and their defined acceptance criteria are considered appropriate for the control of each step of the AS manufacturing process. The bioburden and endotoxins are monitored in appropriate points to assess microbial control. A significant clearance of bioburden and endotoxins is demonstrated in the downstream purification process. PPQ results for USP and DSP have been summarized and analysed for each manufacturing step for relevant process parameters and IPCs. The validation results for AS manufacture were within the established acceptance criteria for the three PPQ batches.

In addition to the PPQ for the manufacturing process, additional studies including resin lifetime study, membrane lifetime study, in-process intermediate hold time validation, buffer hold time validation, extractable and leachable, impurities removal validation, and AS shipping verification were performed. Some of the studies were conducted at commercial scale, while others were performed at small-scale. The data provided is considered acceptable.

Manufacturing process development

Process Comparability

A thorough description of process changes in all manufacturing steps has been provided in the dossier.

Changes are made during the process development. The changes were made to improve the robustness of the process and control of product quality by updating the process controls. and included changes improving clarity of instructions for additional process parameters, defining process controls based on experiment data, tightening ranges of process parameter.

To evaluate the impact on the AS due to the manufacturing process changes comparability assessments were performed. The presented comparability data is thorough, well-presented and supports the comparability between processes.

Process Characterisation

Summary of QA assessment is provided in the dossier including justifications for each QA ranking. The final list of CQAs identified appear reasonable and consistent and is considered acceptable. The process characterisation of insulin lispro AS process was evaluated and the process parameter classifications and in-process controls were classified based on the impact on the defined CQAs. Process characterisation studies were performed for each manufacturing step. The CPP acceptable ranges (i.e. PAR) were developed based on historical data or process characterisation study range. This approach is endorsed. IPC limits for critical IPCs (CIPCs) of each manufacturing step are proposed. This is considered adequate.

Characterisation

Elucidation of Structure and Other Characteristics

The AS insulin lispro is characterised by a variety of analytical techniques. The characterisation included primary sequence, higher-order structure, product-related substances, product-related impurities and major degradation pathways. Also biological characterisation including target binding (IRA/IRB/IGF-1R), receptor phosphorylation, metabolic activity, mitogenic activity and *in vitro* potency (IRB phosphorylation) have been included in characterisation studies. For primary sequence, a full-length aa sequence has been analysed by LC-MS/MS and were consistent with insulin lispro theoretical amino acid sequence.

The panel of characterisation tests includes several orthogonal techniques and is considered sufficient to elucidate the structure and other characteristics of the AS.

Impurities

Variants that have comparable potency to insulin lispro are categorized into product-related substances, and the other variants, that do not have comparable potency or do not have potency data are categorized into product-related impurities.

Clearance of all process-related impurities was demonstrated in the AS from PPQ batches.

Related protein impurities, single-chain precursor and HMWP are controlled at AS release and stability.

Microorganisms (bioburden) and bacterial endotoxins as potential contaminants are controlled during production and monitored at AS release and stability.

2.3.2.3. Specification

The proposed AS specifications include tests required in the Ph. Eur. monograph for insulin lispro, as well as several additional tests and cover general tests, identity, content/activity, purity/impurity and microbial content.

The proposed acceptance limits are according to Ph.Eur. insulin lispro monograph limits or tighter, or justified based on batch data for non-compendial tests. Batch data to justify the proposed limits is provided.

The acceptance criteria are considered adequately justified.

Analytical procedures

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. Method descriptions and validation report summaries have been adequately provided. In-house methods have been developed for many of the compendial methods. For in-house methods established based on Ph. Eur. and USP, method validation was performed. The in-house methods are developed based on the relevant Ph.Eur. and/or the USP monographs. This is considered adequate.

The validation data demonstrate that the methods are suitable for their intended use.

Batch analysis

Batch data has been provided from different process versions. All batch results were in accordance with the AS specification acceptance criteria.

Reference standards

In-house working reference standards (WRS) have been described. The in-house WRSs are sourced from representative AS batches, each from different process version. The WRSs are qualified against Ph. Eur. insulin lispro reference standard.

Release test results, characterisation test results and stability data for current WRSs have been presented. Reference standard qualification protocol for future WRS has been provided. The methods proposed are the same release and characterisation methods as used for current WRSs and are considered adequate. Stability monitoring protocol for future WRSs for annual monitoring is provided and considered adequate.

Container closure

The proposed primary container closure system (CCS) for insulin lispro AS consists of bottles and an adequate description of the container closure system, including schematic drawing and specifications is provided. The material complies with Ph.Eur. and USP. Extractable and leachable studies have been performed and showed no impurities over safety limits. The container closure for AS is considered adequate and the given information is sufficient.

A secondary packaging systemis adequately described.

2.3.2.4. Stability

The primary stability studies include long term (-25°C to -18°C) and accelerated (2°C to 8 °C) stability studies. Long-term stability data is available for batches including PPQ batches. Accelerated stability data is available.

Based on the provided data, all results met the acceptance criteria for long-term stability. No significant change has been observed for quality attributes and safety attributes under long-term storage conditions (-25ºC to -18ºC). According to provided accelerated stability, the HMWP and related proteins were increased.

The Applicant has furthermore conducted supporting stability studies which include stress studies/ forced degradation studies and a photostability study. The stress conditions were shown to influence insulin lispro AS quality. The design of the stress studies is considered acceptable.

The photostability study shows that the AS is light sensitive and has to be protected from light during storage in alignment with Ph. Eur. The stability results met the acceptance criteria for long-term stability, supporting the proposed commercial AS CCS.

The Applicant has committed to a stability program, following a commercial stability protocol.

Overall, the stability of insulin lispro AS has been adequately addressed. Stability studies have been performed in accordance with ICH guidelines and Ph.Eur. monography for insulin lispro in terms of testing frequency and storage conditions. The proposed shelf-life for insulin lispro AS at the recommended storage conditions is supported by primary stability studies, and is considered acceptable.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and Pharmaceutical Development

The finished product is a colorless, sterile solution of insulin lispro presented in 3 mL Type I glass cartridge, assembled into a pen device presented as a disposable, variable-dose, multiple-dose prefilled pen. It is a combination product intended for use with suitable pen needles, via subcutaneous injection.

The finished product contains 100 U/mL insulin lispro. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. To ensure the extractable volume claimed on the label (3 mL) could be withdrawn and administrated, each cartridge is overfilled There is no overage in the formulation of insulin lispro injection.

Pharmaceutical development

The composition of the FP was selected based on the published available information of the reference medicinal product, Humalog.

Formulation changes were made in the early development stage to achieve biosimilarity to Humalog. The formulation has remained unchanged since clinical PK/PD similarity study. The differences in excipient concentrations compared to Humalog are appropriately justified.

Formulation, pH, and zinc robustness studies were carried out to further confirm the selected formulation.

Visible particles were observed during process development. A comprehensive investigation of visible particles was conducted. The Applicant has performed comprehensive assessments with the conclusion that the presence of the particles has negligible impact on product quality, safety, and efficacy. Additionally, the Applicant has appropriately demonstrated that these particles have low risk to impact on device performance or drug delivery. Overall, it can be concluded that the safety profile is similar for insulin lispro FP and for the reference product, Humalog.

Manufacturing process development

The manufacturing process development contains three stages: development stage, clinical stage, and commercial stage. The formulation has been optimized during the early development but has remained unchanged since the clinical stage. The changes from clinical process to commercial process include scaling up and defining tighter process parameters for several process steps. A thorough description of process changes in all manufacturing steps has been provided.

The process changes have been compared in comparability exercises.

A comprehensive comparability assessment was performed. The justification for comparability acceptance criteria is deemed acceptable. The totality of the data presented in the dossier support the comparability claim between development, clinical and commercial processes.

The comparability assessment between filled cartridges and prefilled pens was performed for clinical and commercial process batches. Data presented indicate that pen assembly process does not have adverse influence on FP quality.

The QTPP of insulin lispro injection is based on extensive characterization of the RMP, Humalog. CQA evaluation was performed. The defined CQAs are found relevant and adequate for a recombinant product.

Criticality of process parameters and IPCs was evaluated. Each CPP, non-CPP (NCPP) and key process parameter (KPP) of the DP manufacturing process have been studied within a defined range. The identified CPPs with proven acceptable ranges (PARs) and CIPCs with proposed commercial limits are found acceptable.

Sufficient information is provided for process evolution. Based on the assessment, several factors and PPs were further evaluated at lab-scale either as single factor experiments or as multiple factor design of experiments (DOEs). With information learned from development studies and manufacturing experience, the intended commercial process was defined. Based on comparison of commercial scale batches, a control strategy with tightened process parameter ranges experienced in the PPQ was established during the commercial phase, which is acceptable.

Production scale and lab scale studies are adequately presented. Compatibility between the product and production materials was confirmed. Extractable studies confirm that all detected extractables and elemental impurities are below the defined permitted daily exposure (PDE) for each tested compound.

Materials of the primary CCS are compendial and found adequate. Stability studies demonstrated that CCS is physiochemically compatible with the product. Extractable and leachable studies were conducted in line with

ICH Q3D. Elemental impurities and extractable compounds were shown to be below the limits. No leachables have been identified indicating that the primary CCS is suitable and safe.

Photostability studies indicate that the FP is photosensitive, but the pen injector provides sufficient protection from the light exposure. Furthermore, the primary CCS protects the FP from microbial contamination by maintaining the container closure integrity over the shelf life of the product.

The functionality of the drug device combination was appropriately demonstrated by the primary stability studies and the primary function tests. The suitable needles for insulin lispro prefilled pen are listed in the dossier. The needle compatibility study was performed according to the ISO 11608-2:2022. All presented results met the acceptance criteria demonstrating the compatibility of the needles with the prefilled pen.

Biocompatibility testing and biological risk assessment were adequately performed demonstrating that the prefilled pen can be considered safe for use as directed. Results from accelerated aging study confirmed the functionality of the pen injector device components for the intended maximum shelf life (36 months).

The shipping validation was done. All verification results met the acceptance criteria indicating that the quality of FP and the functional performance of prefilled pen were not impacted by the simulated shipping conditions and environmental stress.

Based on the data presented, the CCS is deemed suitable for the intended use.

The Notified Body (NB) Opinion for medical device was missing and a Major Objection was raised. During the procedure, the NB Opinion has been provided, indicating compliance of the medical device part with Annex I (General Safety and Performance Requirements) of the Medical Device Regulation (EU) 2017/745.

The microbiological control strategy of insulin lispro injection is sufficiently described. A qualified and suitable bacterial endotoxin test (BET) is in place. The Applicant has provided risk assessment for non-endotoxin pyrogens (NEPs). Bacterial endotoxins are tested at release and shelf life, which is acceptable.

The FP contains metacresol as preservative, due to the multi-dose nature of the medicinal product. Antimicrobial effectiveness testing (AET) was performed according to Ph. Eur. 5.1.3, which appropriately confirmed the effectiveness of the preservative. Microbiological integrity has been verified after multiple doses administered under in-use conditions for 28 days.

2.3.3.2. Manufacture of the product and process controls

IL-CSM Clinical Supplies Management GmbH in Loerrach, Germany is responsible for batch release.

Initially, a valid proof of EU-GMP compliance for the AS/FP manufacturer and for the QC testing site were missing and Major Objections were raised. During the procedure, a valid proof of EU-GMP compliance for these sites has been provided.

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

A detailed description of the FP manufacturing process is provided. It includes six steps: compounding and sterilizing filtration, washing and sterilization of container components, aseptic filling and capping operations, visual inspection, pen assembly, and labelling and packaging. The manufacturing process is adequately presented as flowchart and as narrative description including process parameters (PPs) with acceptable ranges and in-process controls (IPCs) with acceptance criteria. No reprocessing and reworking procedure is proposed for the manufacturing process for insulin lispro FP.

Batch formula and calculation formula per batch for insulin lispro injection is adequately presented. Batch numbering system is appropriately described.

Filled cartridges undergo visual inspection. Cartridges with physical defects and with visible particulates are rejected from the batch.

Processing and hold times are clearly defined.

The nature, size and manufacturer of the sterile filters used in series in the manufacturing process has been described. Product-contact components and equipment and their sterilization procedure have been adequately described.

Process controls

The overall control strategy including identification of CPPs and IPCs have been adequately described and is overall found acceptable. Normal operating ranges (NORs) are mainly aligned with PARs or set tighter, which is supported. Description of the methods used to test the IPCs has been provided.

Process validation

PPQ,consecutive batches of filled cartridgesand corresponding batches of pre-filled pens were manufactured using the proposed commercial manufacturing process. Apart from one deviation, all CPPs, IPCs and release results of filled cartridge batches were within predefined acceptance limits.The investigation of the deviation was appropriately described with no meaningful impact on product quality or validation. All release results for pre-filled pen batches met the predefined acceptance criteria. Data presented demonstrate that commercial manufacturing process is operating in a state of control.

The homogeneity of compounding and filling processes were appropriately demonstrated with routine and additional sampling and analysis, and is considered adequately studied and the results acceptable.

Overall, the manufacturing process has been validated and it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Shipping qualification

The shipping qualifications were performed with temperature-controlled containers. Few deviations occurred. The deviations were appropriately investigated, and corrective measures and updated standard operating procedures were implemented. Shipping qualifications are considered validated.

Investigation of the effects of shipping on the quality of FP has been presented and results confirm no effects on product quality due to shipping simulation studies.

2.3.3.3. Product specification

The applicant has provided FP specifications that covers general tests, identity, content/activity, purity/impurity and microbial content. In general, the specification for insulin lispro injection is set according to the ICH Q6B and Ph. Eur. requirements. The proposed specification for release and shelf life, as well as specification change history are appropriately provided.

The acceptance criteria for specifications have been justified and considered acceptable.

Analytical procedures

Several quality attributes are tested with compendial methods with compendial limits which is generally endorsed.

Validation summaries in accordance with ICH Q2 have been presented for all non-compendial in-house analytical procedures, Validation results are acceptable and analytical methods are shown to be suitable for intended purpose.

Batch analysis

Batch analysis data is provided (cartridge and prefilled pen). All batches met the proposed commercial specification.

Characterization of impurities

The product-related impurities include related proteins and HMWPs, which have been characterised and assessed together with the AS.

Process-related impurities include residual solvents, elemental impurities, and nitrosamines. The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product (for filled cartridges and prefilled pens) has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Container closure system

The primary container closure system consists of a 3.0 mL type I glass cartridge completed with a rubber stopper, and an aluminium cap/rubber seal, which are all of compendial quality. Specifications for the three components are in place where certificates of analysis and quality certificates have been provided and found acceptable. The container closure system provides adequate protection from microbial contamination as demonstrated during process validation and stability studies.

The secondary packaging, a disposable pen injector, does not come in contact with the FP. Specifications are in place.

Overall, the information regarding the container closure system is found satisfactory and the control of the container closure system components are acknowledged.

2.3.3.4. Stability of the product

The proposed shelf life of insulin lispro FP is 36 months at 5 °C ± 3 °C.

The claimed shelf life after first use is 28 days at a usage temperature up to 30 °C ± 2 °C away from direct heat and light.

The stability studies were conducted in accordance with the ICH Q1A, ICH Q1B, and Q5C guidelines. The stability protocols are satisfactorily presented.

The stability data is well presented. The analytical procedures used in stability studies are appropriately described.

Long-term stability study

Batches of cartridges have been placed under the long-term stability program. The design of the stability study is found acceptable and tested parameters cover both the quality of the DP and the functionality of the medical device.

All tested parameters seem relatively stable. Overall, data presented meet the acceptance criteria.

Accelerated stability study

The same batches of cartridges and prefilled pens as used for long-term stability studies were placed under accelerated conditions. Study is completed and data is available for all batches.

Overall, clinical, technical and PPQ batches of both cartridges and prefilled pens showed similar behaviour in accelerated conditions.

In-use stability study

In-use stability study was conducted at long-term storage conditions followed by 28 days at in-use conditions (30 °C ± 2 °C, 75% ± 5% RH). Study has been completed and the product is found to have the desired quality after the in-use period of 28 days at in-use conditions.

Stressed stability studies

Stress conditions and stress study protocols are appropriately presented. The data from stress studies demonstrate that insulin lispro is sensitive to high temperature, extreme pH, oxidative stress and light exposure, which all can impact on product quality of insulin lispro injection. These conditions should be avoided during storage and usage, as described in the SmPC.

Post-approval stability protocol is appropriately provided.

In conclusion, the proposed FP shelf-life of 3 years at 5°C ± 3°C is adequately supported by provided data. Also, the in-use stability is appropriately demonstrated for 4 weeks below 30°C, away from direct heat and light.

2.3.3.5. Biosimilarity

Bysumlog has been developed as a biosimilar to Humalog KwikPen (insulin lispro solution for injection for subcutaneous use).

Batches used in the similarity assessment

Proposed biosimilar: Independent lots were included in the biosimilarity assessment consisting of FP manufactured with the clinical process and commercial process.

Concerning RMP, included in the biosimilarity assessment, the amount of reference batches and range of expiration dates is considered comprehensive and acceptable.

The criticality of the Quality Attributes (QAs)

QA´s included in the biosimilarity assessment contain attributes for assay, zinc content, pH, metacresol, aggregation, total related substance, A21 desamido insulin lispro, other deamidations, carbamylation, N-terminal truncation, dehydration, oxidative and hydrolyzation variants, C-terminal extension, acylation, methylation, sum of acidic and basic variants, HIC post peaks, primary/secondary and higher order structures and product-related substances and impurities. Additional biological assays include *in vitro* potency, target binding, receptor phosphorylation, mitogenic and metabolic activity, are assessed in the Comparative Analytical Assessment to demonstrate the similarity. Relevant QA´s are included in the biosimilarity assessment.

Statistical approach

Quality ranges (QR) were defined for all analytical test methods allowing quantitative analysis. Concerning similarity criteria, the QRs were calculated. The age and storage of the Humalog and test product batches used for the establishment of the quality ranges are stated in the dossier.

Analytical methods

Full validation is provided for methods also used in the release test. For the additional characterization methods, acceptable qualification results are provided. Overall, the used methods are considered suitable for their intended used and adequate qualification is performed.

Reference standards

Reference standard qualification is presented. The Applicant has in detail outlined which reference standard was used for quality attribute testing during the Comparative Analytical Assessment.

Quality Attributes		**Test Method**	**Whether Highly Similar**
Assay		RP-HPLC	Yes
Related proteins	Total related substance	RP-HPLC	Yes*
	A21 desamido insulin lispro		Yes
HMWP		SE-HPLC	Yes*
Zinc content		AAS	Yes*
pH		Potentiometric determination of pH	Yes
Metacresol		RP-HPLC	Yes
Total protein content		RP-HPLC	Yes
	Monoisotopic MW	LC-MS	Yes

Primary structure	Peptide mapping and full-length sequencing		LC-MS/MS	Yes
	Disulfide linkage		LC-MS/MS	Yes
			NMR	Yes
	Free thiols		Ellman's assay	Yes
	pI		iCIEF	Yes
Secondary and higher order structures	α-helix		FTIR	Yes*
	β-sheets			Yes
	β-turns			Yes
	Random coil			Yes*
	Fluorescence		Fluorescence spectroscopy	Yes
	Far–UV CD		CD	Yes
	Near–UV CD			
	Oligomer		N-SEC-MALS	Yes*
	Hydrodynamic diameter		DLS	Yes*
	Tm		DSC	Yes
				Yes*
Product related variants	Deamidation variants	Asn^{B3} deamidation-1	RP-HPLC	Yes
		Asn^{B3} succinimide		Yes
		Gln^{A15} deamidation		Yes
		Gln^{A5} deamidation	CEX-HPLC	Yes
		Asn^{B3} deamidation-2		Yes*
		Asn^{B3} deamidation-3		Yes*
	Carbamylation	Phe^{B1} carbamylation	CEX-HPLC	Yes
		Gly^{A1} carbamylation		Yes*
		Phe^{B1} lost	RP-HPLC	Yes*

	N-terminal truncation (B-chain)	$Phe^{B1}Val^{B2}Asn^{B3}$ lost & Gln^{B4} cyclization	CEX-HPLC	Yes
	Dehydration	Asn^{A21} dehydration	RP-HPLC	Yes*
	Hydrolyzation	$Thr^{A8}Ser^{A9}$ hydrolyzation	RP-HPLC	Yes*
	Oxidative variant	Phe^{B25} oxidation	RP-HPLC	Yes*
	C-terminal extension of B-chain	Arg^{B31} extension	LC-MS	Yes
	Acylation	Ser^{A9} acetylation	LC-MS	Yes
	Methylation	Ile^{A10} methylation	LC-MS	Yes
	Sum of acidic peaks and sum of basic peaks		CEX-HPLC	Yes*
				Yes
	Sum of hydrophobic peaks		HI-HPLC	Yes*
Target binding			IR-A binding	Yes*
			IR-B binding	Yes
			IGF-1R binding	Yes*
Receptor phosphorylation			IR-A phosphorylation	Yes*
			IR-B phosphorylation	Yes*
			IGF-1R phosphorylation	Yes
Metabolic activity			Glucose uptake	Yes*
			Glycogen synthesis	Yes*
			Lipogenesis	Yes*
Mitogenic activity			IGF-1R-dependent mitogenicity	Yes*
			IR-dependent mitogenicity	Yes*
In vitro potency			In-cell western	Yes

"Yes" indicates that all the results of GL Insulin Lispro fell within both of QR and min-max range of EU Humalog, supporting the conclusion that GL Insulin Lispro is highly similar to EU Humalog.

"Yes*" indicates that the results of GL Insulin Lispro did not fall within the QR, or min-max range, or both of QR and min-max range of EU Humalog. However, the differences observed do not preclude a demonstration of highly similar between GL Insulin Lispro and EU Humalog, and justification is provided in specific section.

Table 1: Summary of the Comparative Analytical Assessment results

Related variants: In general, the amount of HMWP is lower compared to Humalog batches The slightly lower amount of HMWP in the proposed biosimilar compared to the RMP does not preclude the demonstration of similarity.

The amount of the total related proteins shows consistent lower levels compared to Humalog.The values for A21 desamido insulin lispro are within the min-max and QR.

Charge Variants:Minor differences in the charge variants can be detected between the test and reference batches, all test batches being within the QR limits. Within the test batches slight difference can be seen between the commercial and clinical batches. This is not considered an issue from biosimilarity point of view. The presented minor differences do not preclude similarity claim.

Hydrophopic variants: Within the proposed biosimilar batches, slightly lower results are detected in the test batches intended for commercial scale than in the clinical bathes. This is not considered an issue from biosimilarity point of view.

All the test batches are between the QR limitsThe presented minor differences to RMP values do not preclude similarity claim.

Product Related Substances and Impurities: All the test batches were within the limit. The outliers are related to lower levels of related substances observed in the test batches and do not preclude similarity. Within the proposed biosimilar batches, differences in the clinical vs. commercial batches can be detected, however not considered a concern from biosimilarity point of view.

The Applicant takes the age differences into account when discussing similarity of stability-indicating attributes, i.e. product-related impurities, charge variants, etc., and as the impurity levels are indeed generally lower in the test lots than in the RMP lots.

Zinc content: All the test batches were below the max value and QR upper limit. The outliers are related to lower levels of the zinc content.These presented minor differences do not preclude similarity claim.

Higher order structure:

Difference in the secondary and higher order structure analysis is detected in the DSC analysis for attribute Tm2.This difference in the melting temperature is explained As other structure analysis show similarity between the proposed biosimilar and RMP, the observed difference in the Tm2 is not expected to have a clinically meaningful impact.

The Biological and Functional similarity assessment

Target binging kinetic of IR-A, IR-B and IGF-1R receptors was evaluated. .All IR-A receptor binding results were within the range except one batch having slightly higher relative Ka valueThe presented minor difference does not preclude similarity claim.Concerning the results on IR-B binding, allbatches were within thequality

rangeWith regards to IGF-1 R binding results, one batch had a marginally lower relative Ka valueOne batch was slightly over the max level. These slight differences might be attributed to the method variability and does not preclude similarity claim.Overall, the target binding kinetics support similarity.IR-A/IR-B phosphorylation and IGF-1R phosphorylation were determined. The presented minor difference is not expected to have clinically meaningful effect and does not preclude similarity claim, thus, similar phosphorylation properties can be concluded based on these results. Mitogenic activity (potential safety concerns) was determined. The activation of IGF-1R induced by insulin analogues plays important roles in regulating mitogenic action in cells, which might cause a potential safety concern. These slightly higher results are considered minor and do not raise any concerns on the similarity claim or safety aspects.

Metabolic activity by glucose uptake, glycogen synthesis and lipogenesis was studied. In summary, the detected differences in the results for metabolic activity are considered minor and the metabolic activity between the test and reference product can be considered similar.

In Vitro Potency was tested by assessing IR-B phosphorylation. All batches support the similarity between the proposed biosimilar and EU Humalog. Overall, the biological activity is compared at sufficient levels (receptor kinetics/autophosphorylation and metabolic activity) and reflect the mechanism of action for insulin lispro. The observed differences are minor, adequately justified and not considered to be clinically meaningful. Thus, unlikely to have clinically meaningful effect.

Comparative Accelerated Stability and Forced degradation Study

The proposed biosimilar and the EU Humalog were compared at accelerated stability studies for 6 months at of 25°C±2°C, RH 60% ± 5%. Included analyses are HMWP related proteinsand assay, total protein content, charge variants, hydrophobic variants, oligomer MW, melting temperature, hydrodynamic diameter, product related variants, free thiols, higher order structure and intrinsic fluorescence, target binding (IR-A, IR-B, IGF-1R), phosphorylation (IR-A, IR-B, IGF-1R), *in vitro* potency, mitogenic activity (IR, IGF-1R), and metabolic activity (glucose uptake, glycogen synthesis, lipogenesis).

Results for attributes with notable stability indicating nature (HMWP, related proteins, assay) show slight difference in the levels of HMWP.However, the difference is not considered a major difference.Other slight differences can be observed for higher levels for monomer and Tm but are most probably related to the different content of zinc Thus, as other parameters related to higher order structure and biological activity between the test and RMP do not show major differences, this is not considered to preclude similarity claim and is not expected to have clinically meaningful impact.

Similar observations can be found in the results for comparative forced degradation study as for the comparative accelerated stability studies.

A head-to-head freeze/thaw study was performed to show that thawing C does not impact studied QAs of the product. Freezing/thawing has insignificant impact on relevant physicochemical, structural, and biological QAs. This is acknowledged.

The accelerated and forced degradation studies are considered supportive of a conclusion of biosimilarity.

Overall, the data provided support the conclusion on biosimilarity.

2.3.3.6. Adventitious agents

A major objection was raised for the cell bank. The applicant has performed a risk assessment, done extensive design of experiment process characterisation studies to evaluate the process impact on product quality, as well as introduced an amended control strategy.

Based on the data presented, it is considered that the clearance capacity of the downstream process is considered adequately demonstrated. The analytical methods used for development studies and routine IPC controls and AS release have been qualified or fully validated as applicable. The proposed amended testing strategy is considered comprehensive to control the quality of the product and the major objection was resolved.

A recommendation, on the strategy and timeframe for a post authorisation manufacturing change, is endorsed (REC). Insulin lispro AS is produced by fermentation with *E. coli* having a low risk of contamination with mammalian viruses. The Applicant states that no materials of animal origin are used in the manufacture of insulin lispro AS or FP. For the only animal-derived raw material, appropriate documents have been provided.The overall microbial control strategy for AS and sterility control of FP are deemed appropriate to minimize the risk of adventitious agent contamination.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Bysumlog is a biosimilar to Humalog KwikPen.

Manufacture, development, characterisation and control of AS and FP are adequately described. The proposed AS and FP manufacturing processes are considered justified and the control strategy is considered sufficient to assure consistent and adequate quality of the product.

The major objections initially identified, concerning GMP inspections of manufacturing and testing sites and the missing notified body opinion, were adequately addressed during the assessment by providing adequate documentation.

Raw materials and establishment of MCB and WCB have been appropriately described. A comprehensive control strategy to ensure sufficient quality of drug substance has been presented. The manufacturing process has been appropriately validated. A major objection was raised for the cell bank. Based on the Applicant's comprehensive additional development studies, process characterization studies, development of additional analytic methods, and amended control strategy including IPCs and AS release specification, the major objection was solved. The Applicant's proposal for a post-authorisation manufacturing update is highly endorsed, and the intended timeframe considered acceptable. The issue is laid down in a respective recommendation (REC).

Comparability with the proposed commercial manufacturing process and earlier processes has been adequately shown. The panel of release tests covers relevant aspects of purity, potency, and safety and is in line with the Ph.Eur. monography for insulin lispro. Reference standards are qualified against Ph. Eur. insulin lispro reference standard. The provided stability data support the proposed AS shelf-life.

The finished product is presented in 3 mL glass cartridge assembled into a variable-dose, multiple-dose prefilled pen device. During process development, visible particles were observed. According to the risk assessment, these particles have negligible impact on product quality, efficacy, safety, and drug delivery.

The proposed specification is in general found acceptable and in line with ICH Q6B. A shelf life of 36 months at 5°C ± 3°C when stored unopened and the shelf-life during use (4 weeks at a temperature below 30°C, protected from light), are acceptable.

A comprehensive biosimilarity exercise has been performed for Bysumlog against the EU reference product, Humalog and the results support a conclusion of biosimilarity.

2.3.5. Conclusions on chemical, pharmaceutical and biological aspects

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

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

2.4. Non-clinical aspects

2.4.1. Introduction

An abbreviated non-clinical development package for Bysumlog consisted of IR-A, IR-B and IGF-1R binding and receptor phosphorylation, and metabolic (glucose uptake, lipogenesis, and glycogen synthesis) and mitogenic activity studies to assess the functional similarity of Bysumlog and EU Humalog. The similarity was considered be demonstrated when 100% of Bysumlog lots fell within the quality range (QR) and the min-max range of EU Humalog. The nonclinical studies contained in addition one supportive toxicology/toxicokinetic 4-week rat study.

The *in vitro* functional comparability assays included EU Humalog andBysumlog manufactured with the clinical process and commercial process, which were considered comparable in 3.2.P.2.3 Manufacturing process development. Receptor binding analysis adopted QR testing to compare Bysumlog with EU Humalog.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

Receptor binding and autophosphorylation

The IR-A, IR-B and IGF-1R binding kinetics of Bysumlog and EU Humalog were analysed by surface plasmon resonance (SPR). Results were reported as tabulated summary data of IR-A, IR-B and IGF-1R binding presented as relative Ka/Kd/KD values (range from min to max) and scatter plots, both generated on the basis of sensorgrams. The activation of IR and IGF-1R after binding of insulin lispro was assessed by phosphorylation (autophosphorylation of specific tyrosine residues on Rs) in CHO cells with commercial kits. In addition, the *in vitro* potency of Bysumlog and EU Humalog (and USP/EP RS) was assessed in CHO expressing IR-B cells by In-Cell Western (ICW) immunoassay method that is based on detection of the phosphorylated status of target proteins (here IR-B) using phospho-specific antibodies.

Mitogenic activity

The mitogenic activity was assessed in rat H4IIE hepatoma cells (deficient in IGF-1R expression) and the human osteosarcoma Saos-2 cells (display a high ratio of IGF-1R to IR).

Metabolic activity

The metabolic activity (glucose uptake, glycogen formation, lipogenesis) was assessed with commercial kits in differentiated mature 3T3-L1 MBX adipocytes.

The results of *in vitro* functional studies are summarised below (and are more detailed presented and assessed under the Quality/Biosimilarity) (table 2).

Receptor Binding	**Similar**
IR-A	yes
IR-B	yes
IGF-1R	yes
Receptor Activation / autophosphorylation	
IR-A	yes
IR-B	yes
IGF-1R	yes
ICW *in vitro* potency assay / autophosphorylation	
IR-B	yes
Mitogenic activity	
IGF-1R Dependent	yes
IR Dependent	yes
Metabolic activity	
Glucose uptake	yes

Glycogen Formation	yes
Lipogenesis	yes

Table 2: The results of in vitro functional studies expressed as relative potencies (%) with min - max range

2.4.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions studies were conducted and are not applicable for biosimilar development in accordance with the applicable guidelines (EMEA/CHMP/BMWP/42832/2005 Rev1 and EMEA/CHMP/BMWP/32775/2005 Rev1).

2.4.3. Pharmacokinetics

No dedicated PK studies was performed. The toxicity and TK characteristics of Bysumlog was compared to EU Humalog and US Humalog in 28-day daily singe SC dosing in SD rats (study S14049). Study included immunogenicity assessment.

Validated LC-MS/MS and ECL methods were used to quantify the insulin lispro and formed antibodies against insulin lispro in rat serum (serums collected from the study S14049).

Distribution, metabolism, excretion and pharmacokinetic drug interaction studies are not applicable for biosimilar development in accordance with the applicable guidelines (EMEA/CHMP/BMWP/42832/2005 Rev1 and EMEA/CHMP/BMWP/32775/2005 Rev1).

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

No single dose toxicity studies were conducted. According to ICH guideline S6(R1), 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 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) no *in vivo* single-dose, repeat-dose, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance and other toxicity studies are required. Nevertheless, the Applicant submitted results of a 28-day repeat dose toxicity study.

2.4.4.2. Repeat dose toxicity

A comparative repeated dose toxicology and toxicokinetic (TK) 28-day rat GLP study (S14049) was conducted following subcutaneous administration of Bysumlog and EU Humalog (and US Humalog), 10 and 50 IU/kg/day. All main cohort animals in the toxicity portion were euthanized on Day 29, and recovery cohort animals were euthanized on Day 43 following a 14-day treatment free period (table 3).

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (U/kg/day)

S14049 repeated dose toxicology and TK study (GLP)	SD Rat /male and female/ n=10+5 (recovery)/Group	10, 50 U/kg/day of GL Insulin Lispro, EU Humalog, US Humalog /Subcutaneous	4-week	50 U/kg/day

Table 3: Repeated dose toxicology and TK study

The findings of Bysumlog were comparable with those of EU (and US) Humalog. The most common finding at necropsy was the presence of areas of red-brown discoloration in the injection site, incidence being low (≤2 animals in group), in all animals except the vehicle control group. There were 2 mortalities in 50 U/kg EU Humalog group and one in 50 U/kg US Humalog group, likely related to severe hypoglycaemia. There were in general no significant differences in food consumption, ophthalmology, haematology and coagulation parameters, in serum chemistry or urinalysis or microscopic findings between the groups. All microscopic findings were consistent with normal background lesions in this age and strain rats. The kidney weight relative to body weight (BW) was significantly decreased for the 10 U/kg Bysumlog group, and 50 U/kg EU Humalog treated female animals compared to vehicle controls. Ovary BW ratio was increased in 50 U/kg EU Humalog females compared to controls. Liver weight, liver-to-BW, spleen, and spleen-to-BW were significantly lower in 50 U/kg EU Humalog male animals compared to controls. No histopathology findings were observed in these organs/tissues correlating to organ weight changes.

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

Anti-drug antibodies were analysed at 29 days after once daily SC injections and on recovery day 15. A large positive ratio variation ranging from 30% to 87.5% was noted, but the immune responses were in general comparable in the treated rats treated with Bysumlog or Humalog (EU and US) after 28 days of daily administration and after two weeks recovery period.

2.4.4.3. Toxicokinetic data

On Day 1 the C_{max} increased from 4.2 to 5.1 folds and AUC_{last} from 6.8 to 7 folds from 10 U/kg to 50 U/kg. On Day 28, plasma insulin C_{max} increased from 3.6 to 3.9 and the AUC_{last} from 3 to 7.2 folds. C_{max}, AUC_{last} and $AUC_{0-\infty}$ were dose proportional for all three insulin products Bysumlog, EU Humalog, and US Humalog) (besides the unavailable $AUC_{0-\infty}$ value of 10 U/kg Bysumlog at Day 28 due to insufficient data).

With repeated daily dosing up to Day 28, the systemic exposure of insulin increased for all three tested insulins with $t_{1/2}$ ranging from ~20 min to 170 min. The differences in PK parameters between Bysumlog, EU-Humalog and US Humalog were concluded to be likely due to limited sample size and sparse sampling scheme.

Overall, systemic exposure of insulin of Bysumlog and Humalog insulin (EU and US) after daily SC injection at doses of 10 U/kg and 50 U/kg/day were comparable in their toxicokinetic profiles.

2.4.4.4. Local Tolerance

Local toxicity was assessed in the 28-day repeated dose toxicity study in rats. Mild local irritation was noted at the injection site (dosing area) animals from all groups with the low incidence. No significant differences were noted in the local tolerance for Bysumlog and EU Humalog.

2.4.5. Ecotoxicity/environmental risk assessment

A justification for not submitting the Environmental Risk Assessment report was submitted. Insulin lispro is an insulin analogue (protein product) for the treatment of Type 1 (T1DM) and Type 2 diabetes (T2DM) mellitus. According to the guideline EMEA/CHMP/SWP/4447/00 corr 1, environmental risk assessment is not required for the products comprised of proteins because they are unlikely to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

The Bysumlog pharmacology consisted of array of *in vitro* functional studies. These studies were in general adequate in their sensitivity, specificity, and ability to demonstrate the functional similarity of Bysumlog and the EU Humalog in regards the binding and activation of the target IR-A and IR-B, and IGF-1R and mitogenic and metabolic activity (glucose uptake, lipogenesis, and glycogen synthesis). Further clarification asked on noted divergences between the presented concentration-response curves and the response value scales for glycogen formation for Bysumlog and EU-Humalog was adequately clarified without the impact on the derived relative potency values, or the validity of the assay. These studies are in line with the recommended data requirements described in the guideline for similar biological medicinal products containing recombinant human insulin and insulin analogues. All Bysumlog functional parameters fell within the quality range of EU Humalog.

The studies involved EU-Humalog and Bysumlog manufactured with the clinical process and commercial process. Although the number of Bysumlog used in the comparability assessments was in a lower side, it was considered adequate to demonstrate the functional similarity.

Nonclinical dossier included one 4 week repeated-dose toxicology and toxicokinetic, and immunogenicity study in rats. The key toxicological findings were limited to 3 unscheduled deaths (in EU and US Humalog groups) most likely related to hypoglycaemia. There were injection site findings (with low incidence), and changes in the organ weighs in kidney, spleen, liver and ovary in treatment group animals compared to control animals, and small changes in the haematology or coagulation parameters, ophthalmology, in serum chemistry and urinalysis. These changes were similar in Bysumlog treated and EU Humalog treated animals. It can be concluded that this study did not reveal significant differences in safety profile between Bysumlog and EU (and US) Humalog treated animals. This conclusion is made with the note that small differences between the biosimilar and reference product are in doubt be seen in the toxicology study.

The TK-parameters differed between the Bysumlog and EU Humalog (i.e. such as at Day 28, the AUC_{last} was 4190 ng*hr/mL for GL Lispro and 4820 ng*hr/mL for EU Humalog after dosing up to 50 U/kg). Nevertheless, it was stated, that TK analysis was not designed to comprehensively assess T_{max} and PK/TK profiles, but to provide preliminary TK information to facilitate the comparison and interpretation of safety findings. Sampling scheme was sparse with limited number of animals which could increase the inter-animal variation. Overall, the TK analysis in the similarity demonstration of Bysumlog and EU Humalog are considered of limited value.

The antibody against insulin lispro analysis did not reveal significant differences between the Bysumlog and EU Humalog animals, but the value of the analysis is limited. The comparison of the ADA response to the biosimilar and the reference product in an animal model is in general not recommended as part of the biosimilar comparability exercise, due to the low predictivity for the immunogenicity potential in humans.

2.4.7. Conclusion on the non-clinical aspects

Available non-clinical data consisting of *in vitro* functional comparative studies (and supportive 4-week rat toxicity/TK study) support the biosimilarity of Bysumlog versus the EU Humalog reference product.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

- **Tabular overview of clinical studies**

No phase 3 trials have been conducted for this application, and none is required for biosimilar insulins as per the guideline [EMEA/CHMP/BMWP/32775/2005_Rev. 1]. No studies in patients with diabetes are included in the application.

One study was included in the clinical development for this application. Details of the Phase 1 PK/PD similarity study in healthy males are given in Table 4 below.

Study/Phase	Objectives	Subject Population	Endpoints	Location of Study Report
PK/PD similarity study (GL-LSP-1006)	To compare the PK and PD profile of GL Lispro with that of EU Humalog and US Humalog.	Healthy male subjects	Primary Pharmacokinetic Endpoints: • $AUC_{ins.0-12h}$, (area under curve) • $C_{ins.max}$ Primary Pharmacodynamic Endpoints: • $AUC_{GIR.0-12h}$, (Glucose infusion rate) • GIR_{max} Secondary Pharmacokinetic Endpoints: • $AUC_{ins.0-2h}$, $AUC_{ins.0-4h}$, $AUC_{ins.0-6h}$, $AUC_{ins.6-12h}$, $AUC_{ins.0-inf}$. • $t_{max.ins}$, $t_{50\%-ins(early)}$, $t_{50\%-ins(late)}$, $t_{½}$, λz. Secondary Pharmacodynamic Endpoints: • $AUC_{GIR.0-2h}$, • $AUC_{GIR.0-4h}$, • $AUC_{GIR.0-6h}$, • $AUC_{GIR.6-12h}$, • $t_{GIR.max}$, • $t_{GIR.50\%-early}$, • $t_{GIR.50\%-late}$, • Time to onset of action	5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Table 4: PK/PD similarity study GL-LSP-1006

The Risk Management Plan (RMP) includes the information that Bysumlog was first approved in China and has been marketed since year 2007. The cumulative exposure to insulin lispro (100 U/mL) is estimated by the Applicant to be 88,027 patient-years.

The RMP includes a short description of the earlier clinical studies that have been conducted outside of the EU for Bysumlog in patients with diabetes: one Phase 2 and two Phase 3 and studies. There are no ongoing studies. The Applicant informs that in the Phase 2 study *Lispro 2012 Gan Lee*, the efficacy of Bysumlog was comparable in efficacy and safety to Humalog in subjects with type 1 diabetes (T1DM) and type 2 diabetes (T2DM). The Applicant further states that in the phase 3 randomised, open-label, parallel, multicentre comparison *study 2003L02125 (BJDB002R*) in patients with T1DM and T2DM, with a duration of 12 weeks, Bysumlog showed equivalent safety, efficacy, good tolerability and compliance to Humalog. Finally, in an open-label, Phase 3, comparative, randomised, multicentre clinical *study ID KI/0513-2* in Russia, safety and efficacy were similar for Bysumlog and Humalog, according to the Applicant; and the immunogenicity profiles for the investigational drug and reference drug were the same.

No clinical efficacy and safety studies are required for authorisation of a biosimilar insulin in the EU; and the Applicant confirms that the safety, efficacy, and immunogenicity of Bysumlog were similar to Humalog in the earlier clinical studies conducted in other geographical regions. Therefore, clinical study reports (CSR) of the prior studies are not requested for assessment.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Bioanalytical methods

Following bioanalytical methods were developed and validated for the clinical study GL-LSP-1006:

- quantification of insulin lispro human serum concentration
- quantification of C-peptide in human plasma for assessing endogenous insulin secretion

Quantification of Bysumlog concentration in human plasma

MSIA-LC-MS/MS based method was developed and validated for the quantification of insulin lispro concentration in human plasma by ARC Trinova Ltd, UK. In general, the bioanalytical method was well described and validated according to the relevant guideline. Appropriate CoA for bovine insulin used as reference was provided and the suitability of the internal standard was demonstrated. The performance of the quality controls showed acceptable intra- and inter-run precision and accuracy. The specificity and dilutional linearity met the acceptance criteria and no matrix interference (healthy plasma, haemolysis and lipemia) was observed. No carry-over was observed although it should be noted that according to the ICH M10 guideline the carry-over should be determined by analysing the blank samples not LLOQ samples after the highest calibration standard. The appropriate stability studies including stability of stock solutions, stability of the analyte in matrix (freeze-thaw, bench-top and long-term) and stability of the analyte in processed samples were performed.

The Applicant also performed comparability studies between Bysumlog, EU-Humalog and US-Humalog. The comparability between Bysumlog and EU-Humalog was acceptable. However, there was a lot of variation in the performance of US-Humalog, but no further concerns are pursued since US-Humalog data provides only supportive data for the MAA and is not considered to have major impact in the B/R assessment.

The analysis of clinical samples (GL-LSP-1006) was reliable within the given accuracy and precision ranges. The reasons for repeat analysis were acceptable and the required criteria for incurred method analysis was met.

Quantification of C-peptide concentration in human plasma

C-peptide concentration in human plasma was quantified by sandwich immunoassay. Only partial validation of the method was performed by MLM Medical Labs GmBH and it included calibration curve, accuracy, precision, LLOQ, carry-over and short- and long-term stability. Since C-peptide plasma concentration data provides only supportive data for the MAA full validation data is not requested nor further concerns are pursued.

Clinical PK/PD similarity study (GL-LSP-1006)

The Applicant conducted a PK/PD equivalence study (study GL-LSP-1006) for the demonstration of PK and PD similarity of Bysumlog with both EU Humalog and US Humalog to obtain marketing authorization within each respective market. Study GL-LSP-1006 was a conventional randomized, double-blind, three-treatment, single dose, three-period, crossover, euglycaemic clamp study conducted in healthy adult male subjects. Primary and secondary PK and PD endpoints of the study are summarized in Table 3.3.1.

The 3 investigational medicinal products (IMP; Bysumlog, EU Humalog, and US Humalog) were administered as single dose injections of 0.2 U/kg in a crossover manner in 3 treatment periods with 6 treatment sequences. Blood samples for insulin lispro concentrations were collected over 12 hours post dose. The primary PK endpoints were the area under the insulin lispro concentration curve from 0 to 12 hours ($AUC_{ins.0\text{-}12h}$) and maximum observed insulin lispro concentration within 12 hours post-dose ($C_{ins.max}$).

To address the primary PK objective, PK bioequivalence between GL Lispro and each reference treatment, the data of the primary PK endpoints were logarithmically transformed since insulin lispro concentrations were assumed to follow a log-normal distribution. The log-transformed endpoints were analysed using a mixed-effects model ANOVA with sequence, period, and IMP as fixed effects and subject within sequence as random effect. Within each model the least squares (LS)-means of each IMP as well as the difference between the IMP were estimated together with the corresponding 90% CIs. If the exponentially transformed 90% CIs of the geometric mean ratios of $AUC_{ins.0\text{-}12h}$ and $C_{ins.max}$ fell within the limits of 80.00% to 125.00%, PK bioequivalence would be concluded.

A total of 38 subjects were randomized, 2 of whom discontinued the study after exposure to 1 IMP (US Humalog for both). Thirty-six subjects completed the study and were included in statistical analysis. One subject's PD results of US Humalog were excluded from statistical analysis due to calibration error of the clamp device, but this did not affect the PK and PD results for Bysumlog and EU Humalog.

Visual inspection of the mean plasma insulin lispro concentration-time profiles of Bysumlog, EU Humalog, and US Humalog indicated no major differences between the IMP (Figure 1).

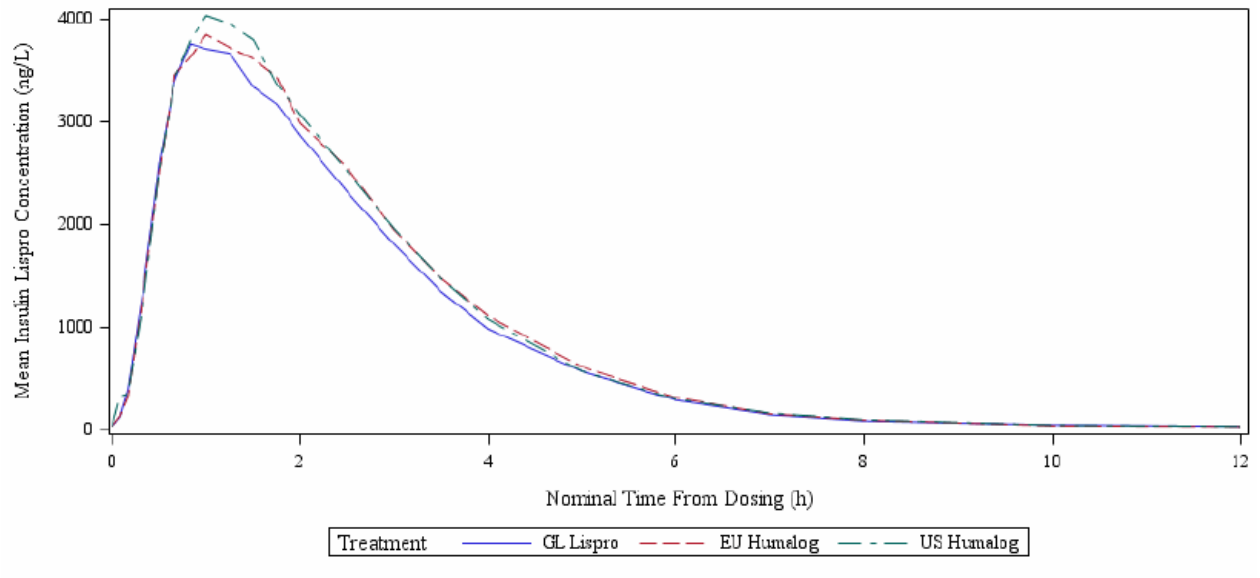

Figure 1: Mean plasma insulin lispro concentration-time profiles after SC administration of GL Insulin Lispro, EU Humalog, and US Humalog (n=36/36/36)

Table 5 shows the results of the statistical analysis of the primary PK endpoints ($AUC_{ins.0-12h}$ and $C_{ins.max}$) for Bysumlog versus EU Humalog. The results of the Primary PK Analysis demonstrate that for both primary PK endpoints the 90% CIs of the ratio of Bysumlog and EU Humalog fell within the limits of 80.00% to 125.00%.

		Geometric LS-Means [1]						
	Analysis [2] (Transformation)	**N**	**GL Lispro**	**N**	**EU Humalog**	**Ratio of LS-Means (%) [3]**	**SD of the Ratio [4]**	**90% CI of the Ratio (%) [5]**
$AUC_{ins.0-12h}$ (h*ng/L)	Primary (Log-transformed)	36	10855	36	11391	95.29	14.59	(92.47, 98.20)
$C_{ins.max}$ (ng/L)	Primary (Log-transformed)	36	4045.7	36	4169.3	97.04	37.27	(89.98, 104.64)

[1]: The Least Squares (LS) Means were estimated based on fitting a mixed-effect ANOVA model to the log-transformed data and back transforming by exponentiation.
[2]: The parameters were log-transformed for analysis and equivalence limits were 80.00% to 125.00%.
[3]: Ratio of the LS-Means are the GL Lispro over EU Humalog multiplied by 100%.
[4]: The standard deviation was estimated using the delta method.
[5]: CI: Confidence intervals for the ratios. The model was based on log-transformed data, and the CI limits were back-transformed from the ANOVA results by exponentiation and multiplied by 100%.

Table 5: Treatment comparison of primary PK endpoints for insulin lispro: GL Insulin Lispro vs. EU Humalog, Primary PK Analysis and Sensitivity PK Analysis

Results for the secondary PK parameters supported the conclusion of PK similarity of Bysumlog and EU Humalog: the median t_{max} was 1.00 h following SC injection of each IMP, and the 90% CIs of the estimated geometric LS-mean treatment ratio were within 80.00% to 125.00% for $AUC_{ins.0-2h}$, $AUC_{ins.0-4h}$, $AUC_{ins.0-6h}$, and $AUC_{ins.0-inf}$. Results of study GL-LSP-1006 also indicated that PK of Bysumlog was similar to US Humalog (data not shown in this AR).

2.5.2.2. Pharmacodynamics

Insulin lispro, like endogenous insulin, binds to the transmembrane insulin receptor that is expressed almost ubiquitously in the cells of the human body. Binding of insulin to the receptor increases glucose uptake in peripheral tissues and inhibition of hepatic glucose production by decreasing gluconeogenesis and glycogenolysis. Further effects induced by insulin include increase in lipid synthesis and decrease in lipolysis and proteolysis.

The pharmacodynamic effect of Bysumlog versus EU Humalog and US Humalog was evaluated using the euglycaemic clamp method in study GL-LSP-1006. During the clamp, blood glucose concentration and the glucose infusion rate (GIR) were continuously measured and recorded using the ClampArt glucose clamp device (Profil Neuss, Germany). The target blood glucose level was 81 mg/dL (approximately 4.5 mmol/L). The glucose clamp device automatically calculated the appropriate adjustments of the intravenous GIR using an algorithm based on the actual measured blood glucose concentration and the grade of variability in the preceding 1 minute. The GIR necessary to keep the blood glucose concentration at the target level was recorded every minute throughout the clamp.

The total amount of glucose infused during the 12-hour clamp [area under the body weight standardized GIR versus time curve ($AUC_{GIR.0\text{-}12h}$)] is a measure of insulin mediated glucose uptake into tissues. $AUC_{GIR.0\text{-}12h}$ and the maximum observed glucose infusion rate within 12 hours post dose (GIR_{max}) were the primary PD endpoints in study GL-LSP-1006.

To address the primary PD objective, PD bioequivalence between Bysumlog and each reference treatment, the data of the primary PD endpoints ($AUC_{GIR.0\text{-}12h}$ and GIR_{max}) were evaluated. The data were not transformed since these parameters were assumed to follow a normal distribution. The Primary PD Analysis based on untransformed endpoints was analysed using a mixed-effects model ANOVA with sequence, period, and IMP as fixed effects and subject within sequence as random effect. Within the model the LS-means of each IMP were estimated and the ratio of the LS-means was determined and then multiplied by 100%. Thereafter Fieller's Theorem for the CI of ratios was used to calculate CIs of the LS-mean ratio. If the 95% CIs of the ratio of $AUC_{GIR.0\text{-}12h}$ and of GIR_{max} fell within the limits of 80.00% to 120.00%, PD bioequivalence between Bysumlog and EU Humalog would be concluded.

PD bioequivalence between GL Lispro and each reference treatment on the log-transformed primary endpoints, $AUC_{GIR.0\text{-}12h}$ and GIR_{max}, was evaluated as Secondary PD Analysis. The same ANOVA used for the Primary PD Analysis but based on logarithmically transformed PD endpoints was applied to find the estimated LS-mean ratios and corresponding CIs. If the 95% CIs of the ratio of log-transformed $AUC_{GIR.0\text{-}12h}$ and GIR_{max} fell within the limits of 80.00% to 125.00%, PD bioequivalence between Bysumlog and EU Humalog would be concluded.

Figure 2 shows the overlaid mean raw and smoothed GIR profiles of Bysumlog, EU Humalog, and US Humalog. Visual inspection of the GIR curves indicated that profiles of the 3 treatments were similar.

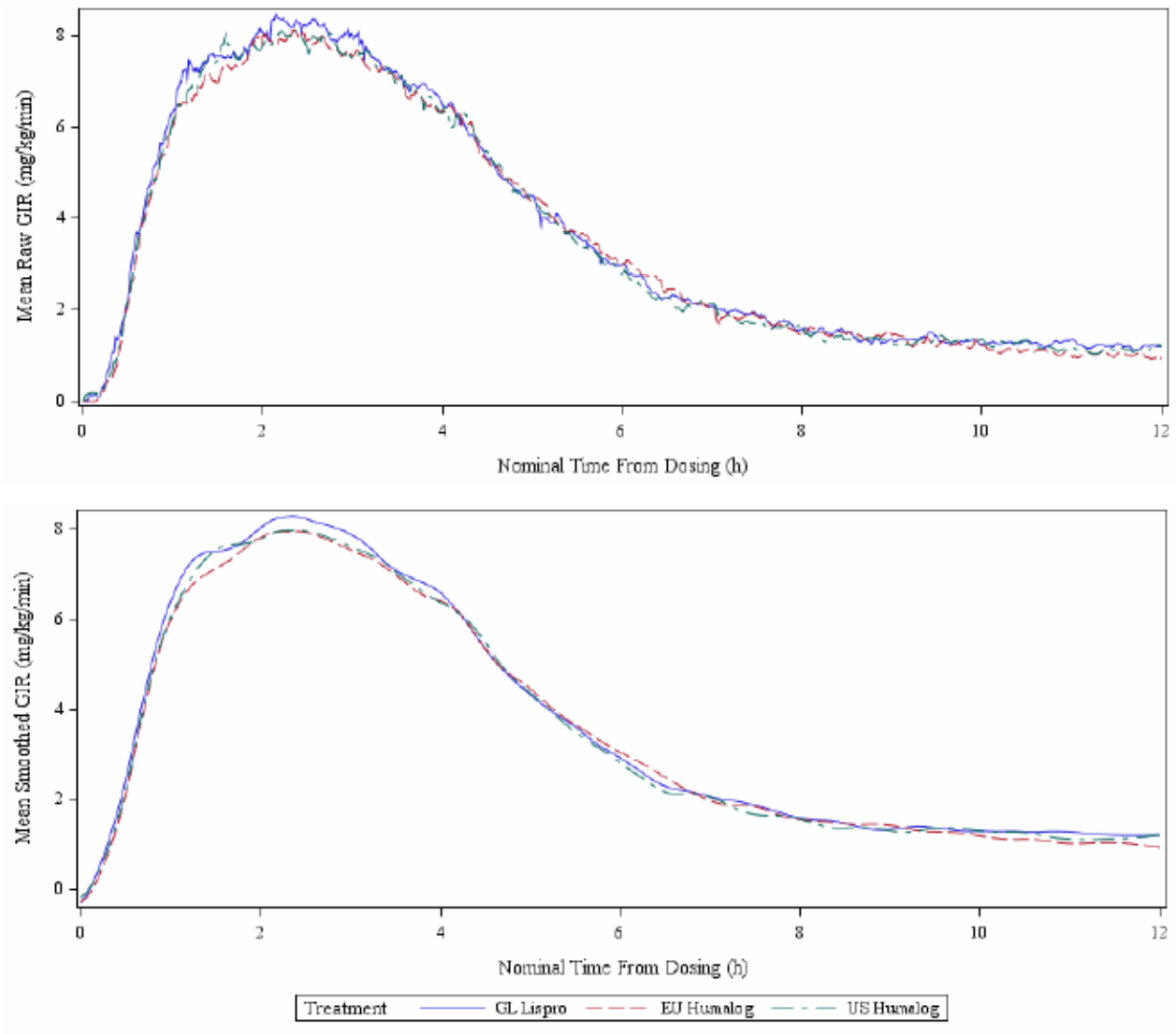

Figure 2: Mean of raw (top) and smoothed (bottom) glucose infusion rate profiles after SC administration of GL Insulin Lispro, EU Humalog and US Humalog (n=36/36/35)

The results of the Primary PD Analysis and Secondary PD Analysis of primary PD endpoints ($AUC_{GIR.0\text{-}12h}$ and GIR_{max}) for treatment comparison of GL Lispro and EU Humalog are presented in Table 6. The results demonstrate that for both primary PD endpoints the 95% CIs of the ratio of Bysumlog and EU Humalog fell within the limits of 80.00% to 120.00% (Primary PD Analysis, untransformed data) and 80.00% to 125.00% (Secondary PD Analysis, log-transformed data).

		LS-Means [1]						
Endpoint	**Analysis [2] / Transformation**	**N**	**GL Lispro**	**N**	**EU Humalog**	**Ratio of LS Means (%) [3]**	**SD of Ratio [4]**	**95% CI of the Ratio (%) [5]**
$AUC_{GIR.0-12h}$ (mg/kg)	Primary (Untransformed)	36	2633.2	36	2549.1	103.30	33.66	(97.25, 109.57)
	Secondary (Log-transformed)	36	2506.6	36	2465.4	101.67	35.02	(93.76, 110.26)
GIR_{max} (mg/kg/min)	Primary (Untransformed)	36	9.49	36	9.17	103.55	37.72	(97.37, 110.07)
	Secondary (Log-transformed)	36	8.97	36	8.70	103.04	41.44	(93.74, 113.26)

Note 1: The Least Squares (LS) Means reported for the Primary PD Analysis were estimated based on fitting a mixed-effect ANOVA model to the untransformed data, while the LS-Means for the Secondary PD Analysis were estimated by fitting the model to the log-transformed data and back transforming by exponentiation.
Note 2: No profiles were excluded from these analyses.
Note 3: Ratio of the LS-Means are the GL Lispro over EU Humalog multiplied by 100%.
Note 4: The standard deviation was estimated using the delta method.
Note 5: CI: Confidence intervals for the ratios. For the Primary PD Analysis, CIs were determined according to Fieller's Theorem. For the Secondary PD Analysis, the model was based on log-transformed data, and the CI limits were back-transformed from the ANOVA results by exponentiation and multiplied by 100%.

Table 6: Treatment Comparison of Primary PD Endpoints:
GL Insulin Lispro vs. EU Humalog, Primary PD Analysis and Secondary PD Analysis.

Results for the secondary PD parameters supported the conclusion of PD similarity of Bysumlog and EU Humalog: the median time to maximum glucose infusion rate ($t_{GIR.max}$) was 2.425 h and 2.375 h following SC injection of Bysumlog and EU Humalog, respectively, and the 95% CIs of the estimated geometric LS-mean treatment ratio were within 80.00% to 120.00% for $AUC_{GIR.0-2h}$, $AUC_{GIR.0-4h}$, $AUC_{GIR.0-6h}$, and $AUC_{GIR.6-12h}$ (primary analysis, untransformed data). Results of study GL-LSP-1006 also indicated that PD of Bysumlog was similar to US Humalog (data not shown in this AR).

The clamp quality parameters precision (coefficient of variation, CV[%]) and deviation from target blood glucose were calculated based on all raw measurements of the per protocol set (n=36) during the 12 hour clamp procedure where GIR was >0 mg/kg/min as pre-defined in the statistical analysis plan. Results in both precision and deviation from target demonstrate that the clamp performance was good and comparable among the tested IMP (Table 7). All subjects met the individual precision requirement (CV% <15%) and the deviation from target requirement (within the range of ±10 mg/dL).

Parameter	Treatment	N	Arithmetic Mean	SD	Min	Median	Max
Precision (CV, %)	GL Insulin Lispro	36	4.65	1.366	1.9	4.54	7.9
	EU Humalog	36	5.16	1.475	2.8	4.89	10.5
	US Humalog	36	5.00	1.770	2.6	4.62	10.6
Deviation from Target (mg/dL)	GL Insulin Lispro	36	0.15	0.348	-1.1	0.18	0.7
	EU Humalog	36	0.11	0.301	-1.1	0.11	0.7
	US Humalog	36	0.32	0.413	-0.2	0.18	1.5

Table 7: Descriptive Statistics for Quality of Clamp Data (PPS)

2.5.3. Discussion on clinical pharmacology

The design of study GL-LSP-1006, including blinding, population (healthy men), insulin lispro dose, pre-study and within-study fasting, target blood glucose level, duration of clamp, and primary PK and PD endpoints is in accordance with the *Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues* and scientific advice given by the CHMP.

Bioanalytical methods

Bioanalytical method for quantification of insulin lispro (MSIA-LC-MS/MS) concentration in plasma was developed and validated in acceptable manner according to relevant guideline. Method for quantification of C-peptide plasma concentration (sandwich immunoassay) was only partially validated but this is adequate since the data is only supportive for the MAA.

Pharmacokinetic results

The point estimates [90% CIs] of treatment ratio for Bysumlog vs. EU Humalog for the primary PK endpoints $AUC_{ins.0\text{-}12h}$ and $C_{ins.max}$ were 95.29% [92.47% to 98.20%] and 97.04% [89.98% to 104.64%], respectively. The results for the primary PK endpoints indicate similar pharmacokinetics between Bysumlog and EU Humalog following SC injection and support the conclusion of biosimilarity. Results for the secondary PK endpoints also support the conclusion of biosimilarity.

Pharmacodynamic results

The point estimates [95% CIs] of treatment ratio for Bysumlog vs. EU Humalog for the primary PD endpoints $AUC_{GIR.0\text{-}12h}$ and GIR_{max} were 103.30% [97.25% to 109.57%] and 103.55% [97.37% to 110.07%], respectively, in the Primary PD Analysis using untransformed data; results for the Secondary PD analysis using log-transformed data were comparable with the Primary Analysis. The results for the primary PD endpoints indicate similar pharmacodynamics between Bysumlog and EU Humalog and support the conclusion of biosimilarity. Results for secondary PD parameters also support the conclusion of biosimilarity.

2.5.4. Conclusions on clinical pharmacology

Results of the PK/PD study GL-LSP-1006 support biosimilarity of Bysumlog versus the EU reference product Humalog.

2.5.5. Clinical efficacy

No phase 3 efficacy and safety studies have been conducted for the current marketing authorisation (MA) application on Bysumlog.

The Applicant originally planned to conduct one phase 3 comparative study "GL-LSP1-3003: An Open-label, Randomized, Multicenter, Phase 3 Study to Compare the Immunogenicity, Efficacy, and Safety of Bysumlog to Humalog (Insulin Lispro Injection) in adult patients with Type 1 Diabetes Mellitus". In the scientific advice (SA) letter on 26 April 2018, however, the CHMP answered the Applicant's questions on the proposed phase 3 study

protocol but also commented that specific efficacy studies are not needed for biosimilar insulins, according to the *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]. Consequently, the Applicant did not conduct the planned phase 3 study.

The Applicant confirms that the safety, efficacy, and immunogenicity of Bysumlog were similar to Humalog in the earlier clinical studies conducted in other geographical regions.

Omission of phase 3 efficacy studies from the clinical development of Bysumlog is considered acceptable.

2.5.5.1. Supportive study(ies)

The Applicant has provided two documents related to usability of the pen device: the *Gan & Lee Lispro UnoPen Human Factor Engineering Comparative Analysis* and the *Use Related Risk Assessment* (URRA). These relate to safe use of the product and are assessed in Section 3.3.7.10 of this AR.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data and additional analyses

No phase 3 efficacy studies have been conducted for the current MA application and none is required for a biosimilar insulin according to the *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].

The Applicant has previously conducted one phase 2 and two phase 3 trials outside of the EU. The Applicant confirms in the RMP that the efficacy and safety of Bysumlog was similar to that of Humalog in these studies.

Clinical study reports of the studies conducted in geographical areas outside of the EU are not requested for assessment, since endpoints used in such studies are not considered sensitive enough to detect potentially clinically relevant differences between two insulins. Furthermore, according to the Applicant, no specific issues requiring consideration were found in those studies.

2.5.7. Conclusions on the clinical efficacy

No phase 3 efficacy studies were conducted for the current MA application, and none is warranted for a biosimilar insulin.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

A total of 36 healthy men were exposed to a single dose (0.2 U/kg) of Bysumlog (insulin lispro), EU Humalog, and US Humalog in the PK/PD study GL-LSP-1006. Two additional men were exposed only to a single dose of US Humalog.

2.5.8.2. Adverse events

Overall, 36 adverse events (AEs) were reported during study GL-LSP-1006. All AEs were mild or moderate and had the outcome recovered/resolved. Most frequent AE based on the PT level were headache (3 events after Bysumlog (insulin lispro), 7 events after EU Humalog, and 2 events after US Humalog administration).

2.5.8.3. Serious adverse event/deaths/other significant events

No death, serious adverse event, and other significant event occurred in study GL-LSP-1006.

2.5.8.4. Laboratory findings

There were no relevant changes in laboratory findings from baseline to follow-up in study GL-LSP-1006.

2.5.8.5. Immunological events

No specific clinical immunogenicity study was conducted for Bysumlog (insulin lispro). The Applicant discontinued a planned phase 3 immunogenicity comparative study GL-LSP1-3003 before any patients were recruited, after receiving scientific advice from the EMA and FDA indicating that a comparative clinical immunogenicity study generally would be considered unnecessary to support biosimilarity or interchangeability of insulin products if the comparative analytical assessment adequately demonstrates "highly similar" profile.

The Applicant provided an Integrated Summary of Immunogenicity (ISI), which included immunogenicity risk analysis data from analytical similarity, chemistry, manufacturing, and controls (CMC), visible particles risk assessment, and product-specific risk factors, including, e.g., product-related impurities and product-related substances, immunogenic potential or raw materials, excipients, etc. These issues are reflected in the Quality section. One nonclinical study was conducted. However, the comparison of the ADA response to the biosimilar and the reference product in an animal model is in general not recommended as part of the biosimilar comparability exercise due to the low predictivity for the immunogenicity potential in humans. No concerns regarding immunogenicity were identified in the assessment of physicochemical and functional properties and PK/PD profile of Bysumlog (insulin lispro).

The data from the phase I PK/PD study *A Glucose Clamp Trial Investigating the Biosimilarity of Bysumlog (Insulin Lispro 100 U/mL) with US-Licensed Humalog and EU-Approved Humalog Comparator Products in Healthy Male Subjects (GL-LSP-1006)* was used for biosimilarity assessment between Bysumlog with EU Humalog and US Humalog. The study GL-LSP-1006 included no immunogenicity assessment. This is deemed acceptable. Firstly, in clinical trials, antibody response to new insulins has typically occurred at around 6 months, therefore, an insulin clamp study would not be able to capture the antibody response. Secondly, even though a great majority of type 1 diabetic subjects and a marked proportion of type 2 diabetic subject have anti-insulin antibodies, type 1 diabetic subjects even prior to onset of diabetes, anti-insulin antibodies to analogue and human insulins are in general not related to clinical efficacy or safety according to scientific literature.

2.5.8.6. Discontinuation due to adverse events

No subject discontinued study GL-LSP-1006 due to adverse events.

2.5.8.7. User-related aspects of pen device

The Applicant provided two documents related to usability of the pen device: the *Gan & Lee Lispro UnoPen Human Factor Engineering Comparative Analysis* and the *Use Related Risk Assessment* (URRA).

The URRA document was compiled to identify, analyse, and evaluate reasonably foreseeable risks associated with the use of the Gan&Lee Insulin UnoPen devices by the Applicant for the injection of insulin glargine, insulin lispro or insulin aspart. No usability issues were identified. The Applicant submitted the references for this document with the response, including Human Factor (HF) validation differentiation study reports. Three human factors studies were performed to ensure differentiation of the Bysumlog carton and device from insulin pen injectors and packaging of products containing lispro, aspart and glargine insulin. Based on the human factor differentiation study and the Use-Related Risk Assessment, it was concluded that Bysumlog is sufficiently distinguishable from other insulin pen injectors in terms of use interface. Adequate risk control measures have been implemented to minimize the risk of user errors when using different insulin pen-injectors.

The *Gan & Lee Lispro UnoPen Human Factor Engineering Comparative Analysis* consisted of a physical comparison, a task analysis comparison, and a line-by-line comparison of the proposed Instructions for Use (IFU) and labelling (including pen label and carton box labelling) between the reference product Humalog KwikPen and the Gan & Lee Lispro UnoPen. No HF study was conducted, but the Applicant's comparative analysis was detailed and considered adequate. No issues were identified in this comparison.

Additionally, pictures of currently marketed pen devices and their packages in the EU were included. It was agreed that the proposed orange Bysumlog pen device and the proposed pink carton box of Bysumlog differ sufficiently from the insulin pens currently marketed in the EU and their respective carton boxes.

Notably, there were two other biosimilar insulin products by Gan & Lee Pharmaceuticals Europe GmbHfor which MAA were being assessed in parallel to this application: Dazparda (insulin aspart), biosimilar of Novorapid, and Ondibta (insulin glargine), biosimilar of Lantus. The Bysumlog pen device is orange, with a burgundy dosing knob and a pink pack and pen label. The Dazparda pen device was also planned to be orange, with an orange dosing knob and a lime yellow pack and label. The Ondibta pen was planned to be a white pen device with light blue label and dark blue dose knob and was deemed sufficiently different from the Bysumlog pen. The package of Dazparda was planned to be lime yellow, which is considered sufficiently different from the package of Bysumlog. Since the pen devices of Bysumlog and Dazparda were of the same colour, the Applicant was requested to justify that the Bysumlog pen is distinguishable from the Dazparda pen. The Applicant provided Human Factors (HF) validation differentiation study protocol and report. The participants of the HF study included non-diabetic adolescents, adolescents with type 1 diabetes, adults with type 1 or 2 diabetes, adult day caregivers, health care professionals and pharmacists. The pen devices included 15 different insulin pens with packaging, including currently marketed pens and the Insulin aspart UnoPen, i.e. the Dazparda pen in development. Among 75, two participants made an error for choosing wrong carton, but no one chose incorrect pen in between the several products. The pen device is hence concluded to be distinguishable from the Dazparda pen and other corresponding insulin pen devices.

2.5.9. Discussion on clinical safety

No specific clinical safety studies were conducted, which is in accordance with the 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).

No concerns on safety rose from the PK/PD study GL-LSP-1006. Since insulin lispro is not associated with

clinically relevant immunogenicity, omission of specific immunogenicity studies was deemed acceptable.

2.5.10. Conclusions on the clinical safety

No clinical studies in subjects with diabetes were conducted for the current MA application. It is acceptable as no clinical efficacy and safety studies are required for authorisation of biosimilar insulin products in the EU.

The pharmacodynamics of Bysumlog insulin lispro vs. the reference product Humalog were studied in the PK/PD study GL-LSP-1006. The reported AEs from this study indicated no meaningful safety difference between Bysumlog, EU Humalog, and US Humalog. However, the safety data from a single dose administration in healthy men is of limited value.

Immunogenicity of Bysumlog was not studied in clinical trials for this application. This is in line with the scientific advice given to the Applicant by the CHMP. Antibodies to insulin are very frequent in patients with diabetes but have in general no clinical consequences during treatment with human or analogue insulins. No specific risk for immunogenicity was identified based on the physicochemical and functional characterisation and comparison to the reference product Humalog, and from the comparison of the pharmacokinetic and pharmacodynamic profiles, impurity profile and nature of excipients of Bysumlog vs. Humalog. The Applicant furthermore stated that immunogenicity was similar to Humalog in previous clinical trials conducted outside of the EU.

2.6. Risk Management Plan

2.6.1. Safety concerns

None.

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

None.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.2 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in

the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report to the reference product Humalog solution for injection in a pre-filled pen, as well as Ondibta solution for injection in a pre-filled pen and Dazparda solution for injection in a pre-filled pen that belong to the same device platform. In addition, the applicant submitted user readability testing report covering information in the PI that could not have been bridged to the reference product. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Bysumlog (Insulin lispro) is included in the additional monitoring list as a biological medicinal product authorised in the EU after 1 January 2011.

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

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Bysumlog (insulin lispro), was developed as a biosimilar to the EU reference product Humalog. The Applicant sought approval for the same indications as those approved for Humalog:

> For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Bysumlog is also indicated for the initial stabilisation of diabetes mellitus.

A comprehensive biosimilarity exercise was performed for Bysumlog (insulin lispro) against the EU reference product, Humalog. EU Humalog lots acquired over a timeframe that spans the expiration dates were included. Several lots of Bysumlog were tested. The independent lots were included in the biosimilarity assessment, consisting of FP manufactured with the clinical process and commercial process, which were considered comparable.

Quality ranges (QR) were defined for all analytical test methods allowing quantitative analysis. Concerning similarity criteria, the QRs were calculated as mean ±X SDs.

The comparative testing included analysis of biological activity, primary structure, higher order structure, aggregates, product-related substances and impurities, general properties and thermal stability and degradation studies. Appropriate analytical methods have been utilized to ensure an understanding of the insulin lispro (EU) product profile and of the developed Bysumlog product.

The non-clinical *in vitro* data package consisted of functional studies assessing the binding and activation of the target IR-A and IR-B, and IGF-1R, and mitogenic and metabolic activity (glucose uptake, lipogenesis, and glycogen synthesis). The non-clinical *in vivo* data consisted of one 28-day rat GLP repeated dose toxicity and toxicokinetic study.

The pivotal and only clinical study is study GL-LSP-1006, A Glucose Clamp Trial Investigating the Biosimilarity of Bysumlog with both EU-approved and US-licensed Humalog in Healthy Male Subjects. This was a Phase I single-centre, randomized, double-blind, 3-treatment, 3-period crossover PK/PD comparability trial.

The development plan followed the 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).

3.2. Results supporting biosimilarity

Quality:

Similarity between Bysumlog and EU Humalog has been demonstrated for the physicochemical and biological properties (primary structure, Higher order structure, General properties (including assay, related proteins, HMWP, Zinc content, pH, Metacresol, Total protein content), product-related variants, thermal stability and degradation studies and biological activity (target binding (IR-A, IR-B and IGF-1R); receptor phosphorylation (IR-A/IR-B phosphorylation and IGF-1R phosphorylation); metabolic activity (glucose uptake, glycogen synthesis and lipogenesis);mitogenic activity (IGF-1R-dependent activity, IR-dependent mitogenicity);*in vitro* potency).

Non-clinical:

In vitro functional comparative studies support the biosimilarity of Bysumlog to the EU (and US) Humalog reference product in regards to binding to target IR-A and IR-B, and IGF-1R, and mitogenic and metabolic activity (glucose uptake, lipogenesis, and glycogen synthesis). 28-day rat toxicology study did not reveal significant differences in the safety profiles of the Bysumlog and EU (and US) Humalog treated animals.

Clinical:

In the clamp study, biosimilarity between Bysumlog and EU (and US) Humalog reference product was demonstrated for both PK ($AUC_{ins.0\text{-}12h}$ and $C_{ins.max}$) and PD ($AUC_{GIR.0\text{-}12h}$ and GIR_{max}).

The Applicant adequately justified the absence of an immunogenicity study for this biosimilar insulin lispro product. No risk for immunogenicity was identified in the assessment of physicochemical and functional properties and PK/PD profile of Bysumlog.

3.3. Uncertainties and limitations about biosimilarity

The statistical approach chosen and results of the individual tests of QA´s support a conclusion of biosimilarity. There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

3.4. Discussion on biosimilarity

From the quality point of view, the statistical approach chosen and results of the individual tests of QA support a conclusion of biosimilarity. All biological activities relevant to the primary mechanism of action, including target binding, receptor phosphorylation, metabolic activity and *in vitro* potency, are similar. Additionally, the accelerated and forced degradation studies are considered to support the conclusion on biosimilarity.

The comparative *in vitro* functional studies support the similar functional activity of Bysumlog and the EU (and US) Humalog with regards to the binding to target IR-A and IR-B, and IGF-1R, and mitogenic and metabolic activity (glucose uptake, lipogenesis, and glycogen synthesis).

Clinical PK and PD biosimilarity were demonstrated adequately. As discussed in *Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues*, there is no need for specific clinical efficacy studies for insulin biosimilars.

According to scientific literature, insulin lispro has not demonstrated clinically relevant immunogenicity. The product specific risk factors have been assessed including product origin, product related impurities and substance, process related impurities, quaternary structure/aggregates, formulation, extractable and leachable, excipients, primary packaging, particles and glycosylation/pegylation. All these factors are assessed as low risk on immunogenicity. Thus, from quality point of view, no concerns on immunogenicity are observed. No concerns arose regarding immunogenicity potential of Bysumlog in the functional characterization or in the PK/PD profile . Hence, omission of specific immunogenicity studies is deemed acceptable.

3.5. Additional considerations

Section 6.6 of the Product Information (PI) of Bysumlog states that Bysumlog should not be used if it appears cloudy, thickened, or slightly coloured or if solid particles are visible.

Usability of the Bysumlog pen has been evaluated by the Applicant in detail, and no issues were identified by the Applicant. The Applicant provided acceptable comparison of usability of the Bysumlog pen device compared to the reference product Humalog KwikPen. The appearance of the Bysumlog pen and carton box has been demonstrated to be distinguishable from prefilled insulin pens and carton boxes of currently marketed insulin lispro, aspart and glargine products in the EU. It was also distinguishable from the pen device of the biosimilar insulin aspart in development by the Applicant (Dazparda insulin aspart UnoPen).

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant submitted a critical report, addressing the possible similarity with authorised orphan medicinal products. The claimed indication *"For the treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Bysumlog is also indicated for the initial stabilisation of diabetes mellitus."* overlaps with the orphan drug designation of Amglidia, EU/3/15/1589. Amglidia is approved in the indication *treatment of neonatal diabetes mellitus,* for use in newborns, infants and children.

Bysumlog (insulin lispro) and Amglidia (glibenclamide) are similar based on therapeutic indication, but not similar based on mechanism of action, and principal molecular structure. Therefore, it is concluded that Bysumlog is not similar to Amglidia.

3.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Bysumlog is considered biosimilar to Humalog. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Bysumlog is not similar to Amglidia within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Bysumlog is favourable in the following indication(s):

> Treatment of adults and children with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis. Bysumlog is also indicated for the initial stabilisation of diabetes mellitus.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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

Not applicable.