13 November 2025
EMA/337757/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ondibta

International non-proprietary name: Insulin glargine

Procedure No. EMEA/H/C/006136/0000

Note

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

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List of abbreviations

Abbreviation	Expansion
%	Percent
%(v/v)	Volume concentration
AAS	atomic adsorption spectroscopy
ADA	anti-drug antibodies
AE	Adverse Event
AESI	Adverse event of special interest
AIA	Anti-insulin antibodies
ANCOVA	analysis of covariance
ANOVA	Analysis of variance
ASE	asymptotic standard error
ATCC	American Type Culture Collection
ATP	adenosine triphosphate
$AUC_{GIR.0-24h}$	Area under the GIR curve from 0 to 24 hours
$AUC_{ins.0-24h}$	Area under the plasma insulin concentration curve from 0 to 24 hours
AVG	average
BID	Twice daily
BLA	Biologics License Application
BLGF	break loose and glide force
BMI	Body mass index
BPD	Biologic Product Development
BPCI Act	Biologics Price Competition and Innovation Act
°C	Degree Celsius
C	concentration
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CCk8	cell counting kit-8

Abbreviation	Expansion
CD	circular dichroism
CEX-HPLC	high performance liquid chromatography
CFU/mL	colony-forming units per milliliter
CGM	continuous glucose monitoring
$C_{ins.max}$	Maximum observed insulin concentration
CM	carboxyl methyl
C_{max}	Maximum concentration
CPP	critical process parameter
CQA	critical quality attributes
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLS	dynamic light scattering
DNA	Deoxyribonucleic acid
DO	Dissolved oxygen
DOA	Duration of Action
DOE	design of experiments
DS	Drug substance
DSC	differential scanning calorimetry
DSP	downstream process
EAC	equivalence acceptance criterion
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EIIPD	efficacy-interfering important protocol deviation
ERIPD	Eligibility Related Important Protocol Deviation
ELISA	ELISA
EOP	end of process
EOS	end of shelf life

Abbreviation	Expansion
EU	European Union
EU Lantus	European Union-approved Lantus
FAS	Full Analysis Set
FBG	Fasting blood glucose
FDA	Food and Drug Administration
g/L	Grams per liter
FAS	full analysis set
FBG	fasting blood glucose
FMEA	FMEA
FTIR	fourier transform infrared spectrometer
GCP	Good Clinical Practice
GIR	Glucose infusion rate
GIR_{max}	Maximum observed glucose infusion rate
GL	Gan & Lee
GL Glargine Injection	Gan & Lee Insulin Glargine Injection (Ondibta)
GLP	Good laboratory practice
GMP	Good manufacturing practice
hr	hours
HbA_{1c}	Glycosylated haemoglobin (glycated haemoglobin)
HbA_{1c}	glycosylated haemoglobin
HCP	host cell protein
HED	HD human equivalent dose
HMWP	high molecular weight proteins
HP1	chromatography
HS-GC-MS	HS-GC-MS
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCIEF	imaged capillary isoelectric focusing
ICP-MS	Inductively Coupled Plasma Mass Spectrometry

Abbreviation	Expansion
ICP-OES	Inductively Coupled Plasma - Optical Emission Spectroscopy
IGF-1R	type 1 insulin-like growth factor receptor
INN	International non-proprietary name
IND	Investigational new drug
IMP	Investigational medicinal product
I	impact
IP	Investigational Product
IIIPD	Immunogenicity-interfering important protocol deviation
IPCs	IPCs
IPD	important protocol deviation
IR	Insulin receptors
IR2	insulin receptors 2
IR-A	Insulin receptor A
IR-B	Insulin receptor B
ISI	Integrated summary of immunogenicity
kL	Kiloliter
Ka	Association rate constant
Kd	Dissociation constant
kDA	kilodaltons
KPP	key process parameter
L	liter
L/hr	L/hr
LC-MS	liquid chromatography-mass spectrometry
LC-MS/MS	liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry
LIVCA	limit of *in vitro* cell age
LP1	low pressure cation exchange with carboxyl-methyl (CM) resin
LS	least squares
M1	21A-Gly-insulin

Abbreviation	Expansion
M2	21A-Gly-des30B-Thr-insulin
MA	marketing authorisation
MAH	Marketing Auhtorisation Holder
MCB	Master Cell Bank
MedDRA	Medical dictionary for regulatory activities
mg/mL	Milligrams per milliliter
min	minutes
Mm	micrometer
M	moles
MPa	megapascal
MS	mass spectrometry
mS/cm	mS/cm
NAbs	Neutralising Antibodies
NCA	National Competent Authority
NDA	New Drug Application
NCBI	NCBI
NCPP	non-critical process parameter
NGS	next generation sequencing
nM	nanoMoles
NMR	nuclear magnetic resonance
NOAEL	No Observed Adverse Effect Level
NSAIDs	nonsteroidal anti-inflammatory drugs
N-SEC-MALS	non-denatured size exclusion chromatography multi-angle light scattering
OECD	Organisation for Economic Co-operation and Development
OD	Optical density
OC	outstanding concern
OOF	out of refrigerator
OOS	Out of specification
PARs	PARs

Abbreviation	Expansion
PD	Pharmacodynamics
PFU/mL	plaque-forming units per milliliter
pH	potential of hydrogen
Ph.Eur.	European Pharmacopoeia
Phi80	Enterobacteria phage phi80
PHS Act	Public Health Service Act
PK	Pharmacokinetics
PKC	protein kinase C
PPS	Per Protocol Set
PP bottle	Polypropylene bottle
PP caps	Polypropylene caps
PPCO bottles	polypropylene copolymer bottles
Ppm	Ppm
PPQ	process performance qualification
PPS	per protocol set
Protein/L	Protein per liter
PT	Preferred term
QR	Quality range
Q	Quartile
QAa	QAa
QAs	quality attributes
QC	quality control
q-PCR	q-PCR
QTPP	QTPP
RLD	Reference Listed Drug
RMP	reference medicinal product
RMSE	root mean square error
RP	Reference Product
RP-HPLC	reverse phase-high performance chromatography

Abbreviation	Expansion
RS	reference standard
SAE	Serious Adverse Event
Saos-2 cell	human sarcoma osteogenic cell
SAP	Statistical analysis plan
SC	Sub cutaneous
SD	Standard deviation
SE	SE standard error
SEC-MAL	Size Exclusion Chromatography with Multi-Angle Light Scattering
SE-HPLC	size exclusion-high performance liquid chromatography
SmPC	Summary of Product Characteristics
SOC	System organ class
SOPs	Standard operating procedures
SPR	Surface plasma resonance
SS	safety analysis set
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
T3DB	Toxin and Toxin Target Database
TAMC	total aerobic microbial count
TEAE	TEAE treatment-emergent adverse event
TI	tolerance interval
T_{max}	T_{max}
$t_{max.GIR}$	Time to maximum glucose infusion rate
$t_{max.ins}$	Time to maximum observed plasma insulin concentration
TOR	time of refrigeration
TRP	total related proteins
U	uncertainty
U/mg	Units per milligram
UF/DF	Ultrafiltration/diafiltration
UPLC-DAD	ultra-performance liquid chromatography method with diode array detection

Abbreviation	Expansion
URTI	Upper respiratory tract infection
US	United States
USAN	United States Adopted Name
US Lantus	US-approved Lantus
USP	upstream process
WCB	Working Cell Bank
WHO	World Health Organization
WRS	working reference standards
Zn	Zn

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant Gan & Lee Pharmaceuticals Europe GmbH submitted on 6 July 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Ondibta, 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 diabetes mellitus in adults, adolescents and children aged 2 years and above.

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: Lantus 100 units/ml Solution for injection
- Marketing authorisation holder: Sanofi-Aventis Deutschland GmbH
- Date of authorisation: 09-06-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/134/030

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

- Product name, strength, pharmaceutical form: Lantus 100 units/ml Solution for injection
- Marketing authorisation holder: Sanofi-Aventis Deutschland GmbH
- Date of authorisation: 09-06-2000
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/00/134/030

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: Lantus 100 units/ml Solution for injection
- Marketing authorisation holder: Sanofi-Aventis Deutschland GmbH
- Date of authorisation: 09-06-2000
- Marketing authorisation granted by:
  - Union

- (Union) Marketing authorisation number(s): EU/1/00/134/030
- Bioavailability study number(s): GL GLA-CT-1002

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
31 January 2019	EMEA/H/SA/4001/1/2018/III	Juha Kolehmainen and Kolbeinn Gudmundsson
22 July 2021	EMA/SA/0000056284	Armin Koch and Kolbeinn Guðmundsson

EMEA/H/SA/4001/1/2018/III

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

- The applicant's approach to demonstrate comparability between Drug Substance manufactured by different processes and the corresponding Drug Products; the sponsor's proposed Analytical Similarity Assessment Plan and in particular the assays selected, the proposed test parameters and statistical methods, as well as the sampling plan and the proposed data inclusion/exclusion plan.
- The acceptability of the proposed cell-based assay for evaluation of mitogenic activity and the SPR-based assay for assessing the binding properties to INSR and IGF-1R.
- The adequacy of the proposed clinical development plan to support MAA, including a pivotal phase 1 PK/PD study versus US and EU sourced Lantus and two phase 3 confirmatory studies comparing immunogenicity , efficacy and safety in type 1 and Type 2 DM, also supplemented by another completed phase 1 study comparing PK/PD versus US sourced Lantus; the proposed statistical analysis plan; the assessment of hypoglycaemia incidence as part of the overall safety evaluation.

EMA/SA/0000056284

The Scientific Advice procedure pertained to the following Quality aspects:

- Analytical similarity including the approach for quality range assessment, quality attributes to be

included in the comparative analytical assessment, strategy to address usability engineering requirements for the planned pen device, equivalence of alternate administration devices.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: Nicolas Beix

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Bianca Mulder

The application was received by the EMA on	6 July 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 July 2025
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	27 August 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 September 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	18 September 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 October 2025
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	30 October 2025
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 Ondibta on	13 November 2025
The CHMP adopted a report on similarity of <name of the medicinal	13 November 2025

product with Amglidia on (see Appendix on similarity)	

2. Scientific discussion

2.1. About the product

Ondibta has been developed as a biosimilar to the reference product Lantus. The claimed indication is:

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

The Applicant is claiming the same indication as is approved for Lantus.

2.2. Type of Application and aspects on development

During the development of Ondibta, the applicant sought Scientific advice was obtained from the EMA Scientific Advice Working Party (SAWP) on two occasions.

Clinical:

The Applicant received CHMP scientific advice in January 2019. In the scientific advice, it was mentioned that the clamp study is considered the pivotal study and that the phase 3 studies are considered supportive only. In the advice the EMA emphasised that a non-inferiority margin for HbA_{1c} of 0.3 should be applied. The applicant has analysed the data in a hierarchical order starting with a non-inferiority margin of 0.4 and subsequently used the margin of 0.3. This is acceptable.

It was stated by the CHMP that the pilot clamp study, GL-GLA-001, was considered supportive only, as the Ondibta used was produced and compared against the US manufactured Lantus. The applicant has submitted the study as requested during the pre-submission meeting.

Furthermore, the MAH followed the appropriate recommendations for to analytical biosimilarity assessment in this procedure.

Quality:

The applicant received a pre-submission scientific advice on the protocol for qualification of new working cell bank. In this regard, EMA recommended more clear and specific acceptance criteria for the proposed qualification tests. The applicant has satisfactory applied the recommendations regarding presentation and justification of the data for comparability between DS manufactured by different processes.

The applicant received CHMP scientific advice in January 2019 and follow-up advice in July 2021 concerning the analytical biosimilarity assessment plan. The applicant has complied with the advice to follow the reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017). Overall, the recommendations given to the applicant concerning the approach to analytical biosimilarity assessment have been satisfactorily followed.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as solution for injection in pre-filled pen containing 100 units/ml of insulin glargine as active substance.

Other ingredients are: zinc chloride, metacresol, glycerol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), and water for injections.

The product is available in a 3 ml filled cartridge. The cartridge is sealed in a disposable pen injector.

2.3.2. Active Substance

2.3.2.1. General information

Insulin glargine is a human insulin analogue that consists of two chains. The A-chain is composed of 21 amino acid residues, and the B-chain is composed of 32 amino acid residues. Its primary structure is identical to that of human insulin except that position 21 in the A-chain is Gly rather than Asn and there are two additional arginine amino acid residues at the C-terminal of the B-chain, Arg (B31) and Arg (B32).

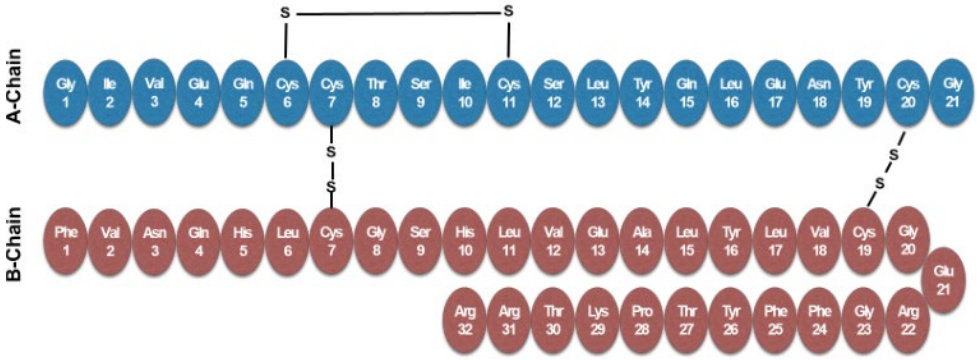


Figure 1: Structure of insulin glargine

2.3.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at Gan & Lee Pharmaceuticals site in Beijing, China. GMP certificate for the site was provided during procedure upon request.

Gan & Lee insulin glargine is produced by recombinant DNA technology, host cell strain *E. coli*. A two-tiered cell bank system including Master Cell Bank (MCB) and Working Cell Bank (WCB) has been established.

Description of manufacturing process and process controls

The active substance manufacturing process has been adequately described. It consists of two stages: the upstream process (USP) and downstream process (DSP).

The active substance manufacturing process is considered acceptable. The description of the manufacturing process is well detailed giving the process parameters and the in-process controls for each step.

The batch numbering systems for both the UPS batches and the DSP batches are well described.

The composition, microbial control, hold times and storage conditions for media, buffers and solutions are described for all the process steps and are acceptable. ***Control of materials***

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. All the raw materials used in manufacture of insulin glargine are listed. The incoming material release specifications were established to demonstrate that the material is suitable for its intended use in the manufacturing process. The media, buffers and solutions are all prepared in-house and steam sterilised or filtered using 0.22 µm filters prior to use. Each have a limited hold time at defined storage conditions. This is endorsed. Lists of the resins used in the chromatography steps is provided and the list of filters and membranes is also provided. This is acceptable.

A two-tiered cell banking system is used, and sufficient information is provided regarding testing of MCB and WCB and release of future WCBs. The clonal recombinant derivative was used to produce the MCB and WCB.

The genetic stability of end of production cells from the three-process performance qualification (PPQ) batches was tested using cell bank release methods. In addition, a limit of *in vitro* cell age (LIVCA) study has been performed to evaluate genetic stability through a passage number greater than the routine cell age in commercial production. The results from the LIVCA study demonstrate that, the cell line is genetically stable and the tested product quality attributes are not affected. The impurity results met the acceptance criteria.

Preparation procedure of WCB was optimized. The procedure for preparing the original WCB and the current WCB are described. The characterisation results for the WCBs prepared by different procedures are provided and the applied tests and the results showed equivalency of the WCBs.

Control of critical steps and intermediates

During the insulin glargine manufacturing process, critical process parameters for each of the manufacturing steps are controlled within predetermined ranges. The output from each process step is monitored by in-process controls. The microbial control includes bioburden reduction filters at key steps, establishment of maximum hold times for in-process intermediates and monitoring of bioburden and endotoxins

The overall control strategy for active substance manufacturing consists of a set of controls derived from current product and process understanding. The development of the control strategy for the insulin glargine active substance manufacturing process was based on critical quality attributes (CQAs), considering the requirements of process design, development and validation together with control at the level of critical process parameters (CPP) and in-process controls (IPCs). Active substance quality is controlled by operating the CPPs within acceptable ranges and by ensuring that critical IPCs are within specified limits.

The final storage conditions and hold times of each intermediate are well described in the dossier. The storage conditions and hold times of the media and buffers used in the insulin glargine manufacturing process are defined and described as well, which is endorsed.

Process validation

Three consecutive commercial scale active substance batches were manufactured for PPQ. Prior to the start of the process performance qualification, the qualification of the facility, equipment and utilities was completed. Additional PPQ supportive studies were performed at small- and commercial scale. A standard

approach to process validation has been taken which is in accordance with the Guideline on process validation for the manufacture of biotechnologically derived active substance and data to be provided (EMA/CHMP/BWP/187338/2014). Sampling during the PPQ followed a pre-defined testing strategy and samples were tested with validated or qualified analytical methods. Process parameters and IPC results were evaluated against the predefined ranges, acceptance criteria or action limits. Overall, the active substance process validation is considered well conducted and acceptable.

The results for the process parameters and IPCs were within the established acceptance criteria for the three PPQ batches.

Intermediate hold times

The intermediate hold times are assessed for impact on physicochemical stability and microbial risk. The risks were evaluated and the hold times were established based on a combination of small-scale physiochemical study, at scale study results and manufacturing need. The microbial quality of the intermediates after hold is tested at commercial scale for the intermediates of high risk of microbial growth according to the results of the conducted risk assessment. The test results demonstrate effective microbial controls within the studied timeframes for the tested intermediates.

Buffer hold times

Buffers considered high for either or both physicochemical and microbial risk were evaluated using either small-scale or at-scale studies. The final established buffer hold time was evaluated through the combination of physical and chemical study results, manufacturing needs and the at-scale validation results. The risk assessment and the physical and chemical study results are considered acceptable.

Extractable and leachable assessment

A risk assessment of product contact materials used in the manufacturing process has been presented and ranked 8 materials with a medium risk as source of extractables. No high-risk material was identified. The medium risk materials were subjected to further assessment mainly based on data provided by the material vendors. The assessed product contact materials were judged by the applicant to be biologically compatible with the product and will not impact the active substance quality and therefore patient safety. The provided data and the methodology of the risk assessment are endorsed.

The test results of all impurities in the validation batches met the acceptance criteria of the corresponding steps. The results are consistent between the three validation batches, showing that the production process of insulin glargine can efficiently remove the impurities.

Conclusion

The active substance manufacturing process has been validated adequately. Consistency in production has been shown on three consecutive full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces the active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development program.

The active substance manufacturing process for insulin glargine was developed in different stages.

The comparability results demonstrate comparable product attributes.

Characterisation

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of insulin.

For characterization of structure and biological characteristics, several active substance batches were tested, along with an internal reference standard (RS), and for comparison, a Ph. Eur. RS lot and a USP RS lot. Characterization results are consistent between active substance batches and the RSs. It can be noted that the same tests were also performed on finished product batches as part of the biosimilarity exercise.

Overall, structure is considered adequately characterized. Primary structure was analysed by mass spectrometry (MS) (non-reduced, reduced, peptide mapping LC-MS, LC-MS/MS (full-length sequencing with 100% coverage, and Edman degradation. Secondary and higher-order structure was characterized by CD, by intrinsic fluorescence spectrometry, and through measuring the isoelectric point by icIEF. This is quite limited, but as mentioned above, testing was also performed on the finished product in the biosimilarity exercise, and this included the additional tests of: secondary structure by FTIR, tertiary structure by DLS and DSC, and quaternary structure by SEC-MALS. Correct disulphide linkage was confirmed by LC-MS/MS.

The biological characterization is considered adequate. Insulin glargine binds the receptors IR-A, IR-B and IGF-1R, causing autophosphorylation, which in turn affects metabolic and/or mitogenic activity. Binding to IR-A, IR-B and IGF-1R was examined by using SPR, with Ka, Kd and KD being determined. Phosphorylation of IR-A, IR-B and IGF-1R was assessed using cell-based assays. IR-B phosphorylation, also by an in-cell Western potency assay. Mitogenicity (IR- and IGF-1R-dependent, and metabolic activity (glucose uptake, glucagon synthesis, lipogenesis), were assessed by cell-based assays.

For product-related substances and impurities, active substance batches was used (same as for characterization of structure and biological characteristics) along with finished product batches derived from those active substance batches. In general, the characterization is considered adequate.

2.3.2.3. Specification

The proposed panel of release and shelf-life tests cover identity, purity, and appearance. In general, the panel of tests are in line with Ph.Eur. monograph 07/2018:2571 and are considered appropriate for routine control of insulin glargine both at release and in stability program.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. The validation data demonstrate that the methods are suitable for their intended use.

The in-house methods are developed based on the relevant Ph.Eur. and/or the USP monographs with modifications to improve method sensitivity and accuracy or specific product characteristics. The description

of the analytical methods is considered sufficient and a comparison between the corresponding compendial method and the in-house method is presented. The differences are justified.

Batch analysis

Batch analysis data batches used in non-clinical study, clinical study, stability studies or PPQ were presented and certificates of analysis for the three PPQ batches are included. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The applicant has established working reference standards (WRS) throughout the development of insulin glargine. The in-house WRSs are sourced from representative active substance. The release and characterisation tests and their results are presented and deemed acceptable.

Reference Standard Qualification Protocol for Future WR is presented and is deemed acceptable.

2.3.2.4. Stability

The applicant has provided a series of stability studies for the shelf-life determination. Based on these studies, the applicant proposes a shelf-life of 36 months when stored at -20 °C ± 5 °C, protected from light. Stability studies have been performed in accordance with ICH guidelines in terms of testing frequency and storage conditions.

The primary long-term stability studies support the shelf-life claim of 36 months when stored at -20 °C ± 5 °C.

The methods used in the stability testing have been validated, and the specifications have been provided. The stability studies are found acceptable for demonstrating the quality of the insulin glargine active substance over the duration of the shelf life.

The photostability study is conducted in compliance with the ICH Q1B guideline and shows that the active substance is light sensitive and has to be protected from light during storage in alignment with Ph. Eur Insulin glargine.

The stress/forced degradation studies consist of four individual studies: a high temperature stress study, a freeze/thaw cycle stress study, a light stress study and a humidity stress study. It was found that high temperature stress, humidity stress, and light stress conditions can pose an impact on the quality. The design of the stress studies is overall found acceptable.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Ondibta is a sterile, clear and colourless solution supplied in a 3 mL Type I glass cartridge that is assembled into a pen device, presented as a disposable, variable-dose, multiple-dose pre-filled pen. It is a combination product intended for self-administration via subcutaneous injection. The combination product is intended for use with suitable pen needles.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The qualitative

composition of the finished product is the same as for the originator Lantus and the proposed commercial formulation is the same as that used throughout product development including all clinical studies.

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 the finished product.

A formulation robustness study was conducted to evaluate the impact on finished product quality.

Manufacturing process development:

Minor changes (scale up and scale up related adaptations) have been introduced to the manufacturing process of the finished product between development, clinical and commercial process. The changes have been compared in two comparison exercises; development process to clinical process (Comparability 1) and clinical process to commercial process (Comparability 2).

Overall, the performed comparability study supports that finished product quality from development, clinical and commercial processes are comparable.

The quality target product profile (QTPP) of the finished product is based on the label of the reference product Lantus and on extensive characterization of the reference product. This is endorsed.

CQA evaluation was performed based on knowledge from two dimensions, including impact (I) on efficacy/biological activity, pharmacokinetics/pharmacodynamics (PK/PD), immunogenicity and safety and uncertainty (U) of the information used to assign each impact ranking. This approach is found acceptable and the defined CQAs are found relevant and adequate for a recombinant product.

Criticality of process parameters was evaluated based on FMEA analysis combining scores of severity, occurrence and detectability of each parameter. Each critical process parameter (CPP), non-critical process parameter (NCPP) and key process parameter (KPP) of the finished product manufacturing process have been studied within a defined range. The identified CPPs for the finished product are presented in the dossier and are found acceptable.

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. The components comply with their relevant monographs of Ph.Eur. The secondary packaging consists of three sub-assemblies: dosing mechanism, cartridge holder and pen cap. The secondary container closure system does not come in contact with the finished product, and the functionality of the medical device is controlled at the release testing and stability testing which ensures compliance with the specification over the duration of the shelf life. A notified body opinion concerning the administration device has been provided.

Materials of the primary container closure system are found adequate. No negative effects were observed on the finished product quality during the stability studies caused by the primary container closure system and was deemed physiochemically compatible. Extractable and leachable studies were conducted and all tested parameters were well below the limits deeming the primary container closure safe regarding elemental impurities.

Photostability studies reveal that the finished product is sensitive to light exposure, but the pen injector can provide protection from the light exposure. Furthermore, the container closure system protects the finished product from microbial contamination by maintaining the container closure integrity over the shelf life of the product.

The functionality of the drug device combination was demonstrated by the primary stability studies and the primary function tests. The functionality tests were conducted under different environmental conditions and under accelerated ageing conditions where all the functionality tests meet the acceptance criteria.

Shipping verification was performed, and the result of the quality parameters all met the acceptance criteria after being exposed to the simulated shipping conditions. The results were comparable to latest stability results of samples, not being exposed to the simulated shipping conditions.

The applicant outlines the microbiological control strategy in terms of material control, process control and testing control. A low endotoxin recovery study found the finished product did not exhibit low endotoxin recovery phenomenon, that applicant suggests that the release/shelf-life testing of the bacterial endotoxin is sufficient to monitor pyrogens of the finished product. This is acceptable.

The finished product is formulated with metacresol preservative, due to the multiuse nature of the medicinal product. This justification by the applicant is found acceptable. Antimicrobial effectiveness testing was performed according to Ph. Eur. 5.1.3 at the lower specification limit, which confirmed the effectiveness of the preservative at the lower specification limit. Microbiological integrity after multiple doses was demonstrated.

The finished product does not need any reconstitution as the finished product is presented as a pre-filled pen, where the pen injector does not come in contact with the finished product. The compatibility of primary packing was demonstrated. In-use stability is presented and demonstrated the integrity of the medicinal product over the in-use period which is also specified in the SmPC.

2.3.3.2. Manufacture of the product and process controls

The finished product is manufactured, quality control (QC) tested, packed and stored at Gan & Lee Pharmaceuticals, Beijing, China. EU-QP-release is conducted by IL-CSM Clinical Supplies Management GmbH, Baden-Wuerttemberg, Germany. All sites are appropriately GMP authorised.

Each step of the manufacturing process is adequately described. The manufacturing process is a standard finished product manufacturing process and consists of thawing of active substance, compounding and final formulation of the finished product, sterile filtration, aseptic filling into sterilized cartridges, visual inspection after which finished product release testing is performed. After release of the cartridges they are assembled into the pen device, labelled and packed.

No reprocessing and reworking procedure is proposed for the manufacturing process for the finished product.

The overall control strategy including identification of CPPs and IPCs have been described in the dossier and is overall found acceptable. A short description of the methods used to test the IPCs has been provided. The methods used to test all other IPCs are the same as those used to the test the final product and have therefore been described and validated in relevant sections of the dossier. The in-process controls are adequate.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. All parameters, in-process testing, and release results met the predefined criteria, demonstrating that the proposed commercial process is operating in a state of control.

The proposed hold time limits are considered adequately validated and are found acceptable.

Cartridges (primary container closure) are sterilized and depyrogenated. Media fills are performed. Bacterial retention capacity of the filters is confirmed.

Shipping qualifications have been performed to demonstrate temperature-controlled shipping during transportation. Shipping qualification by air transportation is considered validated.

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

Shipping by sea transportation has been successfully validated.

2.3.3.3. Product specification

The specification and justification provided for appearance (colour and clarity), pH, extractable volume, container closure integrity, sub-visible and visible particles, bacterial endotoxins, and sterility are acceptable for biological products for subcutaneous injection.

The majority of specifications and methods are used to control both the active substance and the finished product. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

The analytical methods for these tests are compendial and the acceptance criteria are set according to the compendial limits which is generally endorsed.

The related proteins and HMWPs impurity profile of the finished product is the same as that of the active substance.

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. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product 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.

2.3.3.4. Stability of the product

The shelf life of Ondibta 100 units/ml solution for injection in a prefilled pen is 3 years when stored in a refrigerator (2 °C - 8 °C).

Shelf life after first use of the pen: The medicinal product may be stored for a maximum of 4 weeks not above 30°C and away from direct heat or direct light. The prefilled pens in use must not be stored in the refrigerator. The pen cap must be put back on the pen after each injection in order to protect from light.

The shelf life and the in-use storage conditions of the finished product is supported by long term stability data and in-use stability data discussed below.

The stability studies were conducted in accordance with the ICH guidelines. Batches of cartridges (primary container closure system) and prefilled pens (secondary container closure system) were placed under long-term (5℃ ± 3℃, ambient RH) and accelerated (25℃ ± 2℃, 60% ± 5% RH) conditions. Furthermore, the applicant has conducted in-use stability study, time out of refrigeration (TOR) (and label claim) stability study and stress/forced degradation study. The container closure system of all stability batches is identical to the proposed container closure system for routine use.

The stress studies conclude that the finished product is sensitive to high temperatures, oxidative stress, light exposure and extreme pH can pose an impact on the quality of insulin glargine injection, demonstrated by the provided data, and found appropriate. These conditions should be avoided during storage, as described in the SmPC.

The in-use stability study monitors the stability indicating parameters weekly for 28 days at 30℃ ± 2℃ after being stored for 35 months at the long-term condition. This study verifies the quality of the finished product under the in-use condition as per the SmPC.

2.3.3.5. Adventitious agents

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Details of developmental genetics and the establishment of the MCB and WCB are described. The control strategy for the active substance is comprehensive with sufficient control of each manufacturing step. The manufacturing process has been appropriately validated. The lists of raw materials have been provided and are acceptable. The panel of release tests covers relevant aspects of purity, potency, and safety and in line with the Ph. Eur. monograph for insulin glargine. Batch data provided demonstrate that the commercial process is capable of manufacturing a consistent active substance. The provided stability data support the proposed shelf-life of 36 months when stored at -20°C ± 5°C, protected from light.

The presentation proposed for the finished product is 3 mL Type I glass cartridge that is assembled into a pen device. The formulation is based on the reference medicinal product, and its composition is suitable to maintain the quality of the finished product, which is supported by stability studies. The control strategy for the manufacturing process has been outlined and is considered adequate. Process validation has been completed. The panel of release tests covers relevant aspects of purity, potency and safety. The batch data demonstrates that the commercial process is capable of manufacturing the finished product of a consistent quality. A shelf life of 36 months at 5°C ± 3°C and 28 days at a usage temperature up to 30°C ± 2°C is supported.

A comprehensive biosimilarity exercise has been performed for Ondibta against the EU reference product, Lantus. The results of the individual tests support a conclusion of biosimilarity. Observed differences were acceptable.

A notified body opinion concerning the administration device has been provided.

A major objection was raised by CHMP for cell bank. Following comprehensive evaluation and amendment of the control strategy, the major objection was resolved.

2.3.5. Conclusions on the 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.

2.4. Non-clinical aspects

2.4.1. Introduction

Ondibta (insulin glargine) is developed as a proposed biosimilar to the Sanofi Aventis Lantus (insulin glargine). Ondibta is a long-acting human insulin analogue. The proposed indication for Ondibta is identical to that of Lantus and is: to improve glycaemic control in adults and paediatric patients with Type 1 diabetes mellitus and in adults with Type 2 diabetes mellitus. Ondibta follows the same formulation as Lantus, shares the same components and composition of the active and inactive ingredients (e.g. similar amino acid sequence and excipients) in equivalent amounts, and follows the same route of administration.

The non-clinical programme aimed at proving similarity between the EU-approved Lantus and Ondibta. The conducted studies were in accordance with the requirements presented in the EMA CHMP insulin biosimilar guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1), i.e. comparative receptor binding for IR-A, IR-B and IGF-1R (including on-off kinetics), receptor activation (measured as autophosphorylation of IR-A, IR-B and IGF-1R) and metabolic effects (glucose uptake, lipogenesis and glycogen formation). Additionally, mitogenic activity and potency studies were also conducted. As requested by the guideline, these tests were performed *in vitro* since a higher accuracy can be achieved compared to *in vivo*. Nevertheless, an *in vivo* study was also presented characterising the toxicity and toxicokinetic profile following repeated administration of Ondibta for up to 4 weeks in Sprague Dawley rats. However, in this study comparison were made only to the US-approved Lantus, which was acceptable as the study is only considered supportive.

All studies were performed with Ondibta lots used either in the clinical studies or intended for marketing (commercial lots). All PD *in vitro* studies were conducted at the Gan & Lee analytical platform lab, located in No.8, Nanfeng West First Road, Huoxian, Tongzhou District, Beijing, China. The GLP compliant *in vivo* 28-day repeat-dose toxicity study in rats was conducted at Sinclair Research Center, LLC, Auxvasse, USA in June 2015. Method validation reports for the PD *in vitro* studies were submitted and assessed as part of the quality dossier and no concerns were identified.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

Receptor binding affinity

IR-A, IR-B and IGF-1R binding affinity was determined by Surface plasma resonance (SPR). Results were reported as summary data of IR-A, IR-B and IGF-1R binding presented as relative Ka/Kd/KD values in tabulated form and scatter plots, both generated on the basis of sensorgrams. Only selected representative sensorgrams were presented by the applicant.

All of the data points (100%) for the tested Ondibta lots fell within the quality range (QR) of the EU Lantus, indicating high comparability between the two products for all three receptor types. This is clearly visualised

from the scatter plot presentations, where all Ondibta data points for relative Ka, Kd and KD were seen within the dotted lines representing the QR of US- and EU Lantus, respectively.

Association (Ka) and dissociation (Kd) rate constants were determined on the basis of sensorgrams by fitting of the measured curves (unsmooth colour lines) to an exponential function (assumed to be represented by the black lines). For all of the presented sensorgrams, the association part of the curves appeared very well-fitted, whereas the dissociation part is a little less well-fitted, especially for the higher concentrations 200-800 nM. The impact of this observation on the presented results was not addressed by the applicant. However, the magnitude of the deviations was relatively small and considered to be within acceptable fitting variation.

Not all Ondibta sensorgrams were included in the non-clinical part of the dossier and curve fittings for all lots could therefore not be visually inspected. However, based on the method qualification results and the data presented, reviewed sensorgrams were considered representative.

Surface plasma resonance (SPR) is an acceptable method for determining IR-A, IR-B and IGF-1R binding affinity. The choice of concentrations tested appears adequate, as the resulting curves are evenly spaced out over the sensorgram. Ondibta was tested against the EU-approved reference product EU Lantus (EU Lantus), as required in guideline, in addition to the US-approved Lantus (US Lantus). The number of batches tested with relevance for this EMA application is considered sufficient. Furthermore, the tested Ondibta lots are considered representative for the lots used in the clinical studies or for marketing.

Receptor phosphorylation

Receptor phosphorylation activity was determined in Chinese Hamster Ovary-K1 cells overexpressing IR-A, IR-B or IGF-1R after stimulation with diluted concentrations of insulin glargine. High similarity was seen for IR-B and IGF-1R phosphorylation capability between Ondibta and EU Lantus with 100% of the data points within the QR interval.

For IR-A phosphorylation, most of the data points fell within the QR interval of EU Lantus. Comparability for IR-A phosphorylation between Ondibta and EU Lantus is therefore accepted.

Representative concentration-response curves were presented for receptor phosphorylation. The position of the data points generated a relatively well-fitted sigmoid curve, as expected. Additionally, the sigmoid shape of the curves also reflected the sufficiency of the selected concentrations. The fit of the curves is essential for the reliability of the derived potency values and inclusion of all Ondibta and Lantus concentration-response curves in the dossier would have been preferred.

Metabolic activity (glucose uptake, glycogen synthesis and lipogenesis)

In accordance with guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1), three different assays of metabolic activity were performed comparing glucose uptake, glycogen synthesis and lipogenesis between Ondibta and EU Lantus. Results were reported as relative potency % calculated based on dose-response curves.

Pre-adipocytes (3T3-L1 MBX) from a fibroblastic cell line of murine origin, were differentiated to mature adipocytes and incubated with various insulin glargine concentrations. Glucose uptake was measure by the Glucose Uptake-Glo Assay Kit, which utilises a series of enzyme-coupled reactions to measure 2-deoxyglucose 6-phosphate (2DG6P) formed by from 2-deoxyglucose (2DG) that are transported and formed in the same manner as glucose. 2DG6P cannot be modified and hence accumulates in the cells. The cells are then lysed, and luciferin reacts thorough enzyme-coupled reactions to produce a luminescent signal proportional to the concentration of 2DG6P.

Glycogen formation was detected using the Glycogen-Glo Assay Kit, where the glycogen concentration in the sample is proportional with the luminescent signal conducted by series of enzyme-coupled reactions. The same principle was applied for demonstrating lipogenesis in the Triglyceride-Glo Assay Kit, where triglycerides are converted to glycerol and the amount of glycerol is detected by a luminescent signal conducted thorough enzyme-coupled reactions. Overall, the three methods are considered acceptable for evaluation of glucose uptake, glycogen synthesis and lipogenesis, respectively. Furthermore, the tested concentrations appear sufficient and created a sigmoid sharped dose-response curve, as expected. The number of samples tested is considered sufficient for both Ondibta and the reference product EU Lantus.

For glycogen formation and lipogenesis, it was demonstrated that Ondibta is highly similar to the reference product EU Lantus (and US Lantus) with 100% of the data points within the QR of EU Lantus. For glucose uptake all but one sample fell within the QR of EU Lantus, which is considered acceptable for demonstrating similarity. It was argued that the outlier most likely was a result of method variability, as no effect was seen in upstream target receptor binding or the two other downstream metabolic assays using the same lot. This was agreed.

The reported relative potency percentages (%) were calculated based on curve fitting. When visually inspected, the selected representative dose-response curves appeared well-fitted. However, it should be mentioned that it is considered a limitation that not all curves were presented for visual inspection of the fit.

Mitogenic activity

IGF-1R-dependent mitogenic activity was assessed in a human sarcoma osteogenic-2 cell (Saos-2 cell) line displaying high ratio of IGF-1R to IR. Hence, cell growth is mostly initiated through IGF-1R signaling pathway. The Cell Titer-Glo luminescent cell viability assay was used for quantification by measuring the amount of adenosine triphosphate (ATP) proportional to the number of viable cells. Overall, this is considered an acceptable method.

IR-dependent mitogenic activity was assessed in a rat H4IIE hepatoma cell line deficient in IGF-1R expression and dependent on insulin for cell proliferation. Viable H4IIE cells were detected using the cell counting kit-8 (CCK8) measuring a yellow product (formazan) produced in amounts representative of the number of viable cells. As previously addressed in a Scientific Advice, this method is considered acceptable. No additional justification for the choice of CCK8 was given by the Applicant even though it was recommended in the Scientific Advice. However, from the same advice it appeared that the CCK8 method provided the most reliable results. It should be emphasised that only the overall IR-dependent mitogenicity was reported, as the method does not differentiate between IR-A and IR-B activation.

The number of samples tested ("n") are considered sufficient for both Ondibta and the reference product EU Lantus. Selected representative dose-response curves were presented and when visually inspected the curves appeared well-fitted. However, as previously mentioned it is considered a limitation that not all curves were presented for visual inspection of the fit.

Results were reported as relative potency % for IGF-1R- and IR-dependent mitogenic activity. All of the data points (100%) for Ondibta for IGF-1R and IR-dependent mitogenicity fell within the QR of EU Lantus, demonstrating similarity between the two products. However, all tested Ondibta lots still fell within quality range of EU Lantus when re-visualised.

Potency

In vitro potency of Ondibta lots and EU Lantus lots were tested using In-Cell Western assay, which was developed and targeted to assess IR-B phosphorylation through CHO-K1 cells overexpressing IR-B. The method qualification met all acceptance criteria. The dilutions were used for generating the dose-response curves for the *in vitro* potency data. Of note only representative dose-response curves were provided for Ondibta and EU Lantus which does not allow for a full assessment.

All points for Ondibta with respect to *in vitro* potency fell within the quality range of EU Lantus. Hence, the *in vitro* potency was considered similar between Ondibta and EU Lantus.

2.4.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were conducted. The absence of secondary pharmacodynamics studies is acceptable according to guidance (EMEA/CHMP/BMWP/32775/2005_Rev.1).

2.4.2.3. Safety pharmacology programme

No safety pharmacological studies were conducted. Assuming Ondibta is highly similar to EU-approved Lantus, the safety pharmacology of Ondibta is expected to also be similar. 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) safety pharmacology studies are not required.

2.4.2.4. Pharmacodynamic drug interactions

No studies were conducted. The absence of pharmacodynamic drug interactions studies is acceptable according to the guidance.

2.4.3. Pharmacokinetics

Distribution, metabolism, excretion, pharmacokinetic drug interaction and other pharmacokinetic studies are not required in support of similar biological applications. Absorption and exposure of Ondibta compared to US Lantus were evaluated during the repeat-dose toxicity study in rats (study No S12581) to provide preliminary toxicokinetic information. Bioanalytical methods (study Nos VGNLE1400P1, VGNLE1400P2 and VGNLE1402E1) were validated to support the bioanalysis of insulin glargine, anti-insulin glargine antibodies and the metabolites M1 and M2 in the 4-week repeat-dose toxicology study in rats. In addition, method validation reports for the conducted *in vitro* pharmacology studies were submitted and assessed as part of the quality dossier and no concerns were identified.

2.4.3.1. Methods of analysis

A liquid chromatography-tandem mass spectrometry method was developed and adequately validated for the quantitation of insulin glargine and the metabolites M1 and M2 in rat plasma.

An ELISA method was developed and adequately validated for the quantitation of anti-insulin glargine antibodies in rat serum.

The bioanalytical methods validated in the 4-week repeat-dose toxicology study did not include a GLP compliance statement. However, the studies followed the principles of GLP, and the final reports were audited by the Quality Assurance Unit. In addition, the methods were considered suitable in support of the 4-week repeat-dose study. Hence, the status of GLP compliance during the validation of the methods is considered having no impact on the quality of the data generated using such methods.

2.4.3.2. Absorption

Absorption and exposure of Ondibta compared to US Lantus at doses of 0, 8.25 or 27.5 U/kg were evaluated following subcutaneous (s.c.) administration in Sprague-Dawley rats for 28 consecutive days. After a single administration of Ondibta or US Lantus, T_{max} was between 1 and 3 hours. The terminal elimination half-life could not be determined due to insufficient concentration time points after a single dose administration. C_{max}

was doseproportional. As the dose level increased from 8.25 to 27.5 U/kg (1:3-fold), C_{max} increased from 4.96 to 15.3 ng/mL (1:3-fold) for Ondibta and from 5.98 to 18.9 ng/mL (1:3-fold) for US Lantus. AUC_{last} was dose-proportional for Ondibta (15.7 and 46.3 hr×ng/mL; 1:3-fold) but was not dose-proportional for US Lantus (39.2 and 44.3 hr×ng/mL; 1:1-fold). On Day 28 after repeated dosing, T_{max} for Ondibta or US Lantus reached between approximately 1 to 2 hours. The available terminal elimination half-life was approximately 3 hours. As the dose level increased from 8.25 to 27.5 U/kg (1:3-fold), the systemic exposure (C_{max} and AUC_{last}) values were both dose-dependent but less proportional (1:4-7-fold).

Insulin glargine was rapidly metabolised into its two main active metabolites: M1 and M2, with M1 as the dominant metabolite. The toxicokinetic profiles of both metabolites were overall similar between the two insulin products (Ondibta and US Lantus) on both sampling days. On Day 1, both M1 and M2 appeared in plasma 1 hour after administration. M1 was the dominant metabolite. After a single administration of Ondibta or US Lantus, the T_{max} was 2 hours for M1 and approximately 3-4 hours for M2. The terminal elimination half-life ($t_{1/2}$) was approximately 1.5 to 4 hours for M1 and could not be determined for M2. The C_{max} was dose-proportional for both M1 and M2. On Day 28, after repeated dosing, the M2 toxicokinetic parameters were comparable between the two insulin products at 27.5 U/kg. The T_{max} was 1-3 hours for M1 and 3 hours for M2. The available terminal elimination half-life was approximately 2-3 hours for M1 and could not be determined for M2.

No apparent gender differences were seen in the systemic exposures of insulin and insulin-related metabolites.

Since a comparable number of main and recovery animals developed serum anti-drug antibodies (ADA) after treatment with Ondibta or US Lantus, ADA occurrence is not expected to impact toxicokinetics when comparing Ondibta and US Lantus-treated groups.

2.4.4. Toxicology

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 a 4-week repeat-dose study in rats comparing Ondibta to US Lantus.

2.4.4.1. Repeat dose toxicity

In a 28-day repeat-dose GLP study with a 14-day recovery period Ondibta or US Lantus was given to rats (main: 10/sex/group; toxicokinetics: 20/sex/group; recovery: 5/sex/group at 0, 8.25 and 27.5 U/kg) by daily s.c. injection at dose levels of 8.25 or 27.5 U/kg/day and resulted in reduced glucose levels with dose-dependent duration at all dose levels. Three mortalities were noted: one low dose Ondibta rat (toxicokinetic animal) did not recover from anaesthesia after blood collection. Two high dose Ondibta rats were found dead, one on Day 12 (main study animal) and one on Day 24 (toxicokinetic animal). None of the animals had abnormal gross necropsy findings, and it was considered that they most likely died from exaggerated pharmacology i.e. hypoglycaemia. The only test article-related clinical observation was on a high Ondibta male rat. The animal became lethargic after the dose administration on Day 6 which was attributed to insufficient food supply for the animal. There were Ondibta or US Lantus related increased body weight gain

and food consumption, likely compensatory to reduced glucose levels. Increased serum sodium and chloride were observed in both Ondibta and US Lantus after 28-day dosing, compared with vehicle control groups. Differences were also noted in total serum protein, serum calcium, aspartate aminotransferase, and creatine for both Ondibta and US Lantus, compared with vehicle control groups. However, no correlated-findings or trends in erythrocyte, leukocyte, or coagulation parameter values were noted that would suggest an association with exposure to the treatments. Thus, these findings were considered to be treatment-related non-adverse effects. Males at 27.5 U/kg/day US Lantus had an increased incidence of microscopic changes in the heart. Due to the lack of consistent changes in all animals, and the minimal to mild severity of those changes when seen, those were considered to be a manifestation of Murine Cardiomyopathy and were considered an incidental finding.

There were no adverse effects related to Ondibta or US Lantus with respect to ophthalmology, haematology, coagulation, urinalysis, or organ weight parameters in the main or recovery animals. All groups of both genders exhibited similar histopathological changes.

The NOAEL was 27.5 U/kg/day in animals administered with Ondibta or US Lantus. In general, findings were comparable whether animals were given Ondibta or US Lantus and were consistent with the pharmacological action of both products. The findings were of small magnitude and had no toxicological relevance (study No S12581).

2.4.4.2. Toxicokinetic data

Please refer to section 2.4.3.2 Absorption.

2.4.5. Ecotoxicity/environmental risk assessment

In line with guidance the Applicant provided an acceptable justification for not conducting a full Environmental Risk Assessment. Since GL Insulin Glargine is a protein, it is expected to be fully metabolised into smaller peptides and amino acids via catabolic pathways in the body with negligible excretion of intact, biologically active protein. In accordance with Guideline on the Environmental Risk Assessment for medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev.1 -Corr.), Ondibta is therefore considered to be not hazardous to the environment and no special precautions in terms of use and disposal are needed.

2.4.6. Discussion on non-clinical aspects

The non-clinical programme aimed at proving similarity between the EU-approved Lantus and Ondibta. The conducted studies were in accordance with the requirements presented in the CHMP insulin biosimilar guideline (EMEA/CHMP/BMWP/32775/2005_Rev.1), i.e. comparative receptor binding for IR-A, IR-B and IGF-1R (including on-off kinetics), receptor activation (measured as autophosphorylation of IR-A, IR-B and IGF-1R) and metabolic effects (glucose uptake, lipogenesis and glycogen formation). Additionally, mitogenic activity and potency studies were also conducted. As requested by the guideline, these tests were performed *in vitro* since a higher accuracy can be achieved compared to *in vivo*. Nevertheless, an *in vivo* study was also presented characterising the toxicokinetic and toxicity profile following repeated administration of Ondibta for up to 4 weeks in rats. However, in this study comparison were made only to the US-approved Lantus.

All studies were performed with Ondibta lots used either in the clinical studies or intended for marketing (commercial lots).

Pharmacology

Receptor binding affinity was assessed based on surface plasma resonance (SPR) technology using the Biacore system. Overall, the results showed similarity for IR-A, IR-B and IGF-1R binding affinity when comparing Ondibta with the EU-approved reference product Lantus.

Receptor phosphorylation activity was determined in Chinese Hamster Ovary-K1 cells overexpressing IR-A, IR-B or IGF-1R after stimulation with diluted concentrations of insulin glargine. Based on the presented results, similarity was seen for IR-A, IR-B and IGF-1R phosphorylation capability between Ondibta and EU Lantus. Hence, comparability for IR-A phosphorylation between Ondibta and EU Lantus was accepted.

Pre-adipocytes (3T3-L1 MBX) were differentiated to mature adipocytes and incubated with various insulin glargine concentrations. Insulin glargine-stimulated glucose uptake, glycogen formation, and lipogenesis were assessed using Glucose Uptake-Glo Assay Kit, Glycogen-Glo Assay Kit and Triglyceride-Glo Assay Kit, respectively. Overall, similar metabolic activity was demonstrated between Ondibta and the reference product EU Lantus with respect to glucose uptake, glycogen formation, and lipogenesis. This is agreed by the CHMP and comparability between Ondibta and EU Lantus for glucose uptake was accepted.

IGF-1R- and IR-dependent mitogenic activity was determined in a human osteosarcoma Saos-2 cell line, and in a rat H4IIE hepatoma cell line by Cell Titer-Glo luminescent cell viability assay and Cell Counting kit-8 (CCK8), respectively. Similar IGF-1R-dependent mitogenic activity was demonstrated between the tested Ondibta lots and the reference product EU Lantus.

In vitro potency of Ondibta lots and EU Lantus lots were tested using In-Cell Western assay, which was developed and targeted to assess IR-B phosphorylation through CHO-K1 cells overexpressing IR-B. All points for Ondibta with respect to *in vitro* potency fell within the quality range of EU Lantus. Hence, the *in vitro* potency was considered similar between Ondibta and EU Lantus. Of note, only representative dose-response curves were provided for Ondibta and EU Lantus which does not allow for a full assessment. However, based on the quality of the submitted curves, this is considered acceptable.

Overall, the *in vitro* methods selected to represent the pharmacology part of this biosimilar application were considered acceptable and number of samples tested sufficient for the number of Ondibta lots and EU Lantus lots included in the different studies. Method validation reports were submitted and assessed as part of the quality dossier and no concerns were identified.

Pharmacokinetics

Distribution, metabolism, excretion, pharmacokinetic drug interaction and other pharmacokinetic studies were not required in support of similar biological applications.

Absorption and exposure of Ondibta compared to US Lantus were evaluated during the repeat-dose toxicity study in rats to provide preliminary toxicokinetic information. Overall, the assessment of systemic exposure of insulin glargine for Ondibta and US Lantus at doses of up to 27.5 U/kg/day did allow for comparability.

To ensure meaningful data interpretation, the standard deviation should have been calculated for the toxicokinetic parameters. However, this did not affect the study outcome and the Applicant stated that the toxicokinetics of the study was not designed to comprehensively assess the toxicokinetic profile of Ondibta, but only to provide preliminary toxicokinetic information.

Bioanalytical methods were adequately validated to support the bioanalysis of insulin glargine, anti-insulin glargine antibodies and the metabolites M1 and M2 in the 4-week repeat-dose toxicology study in rats.

Toxicology

According to existing guidance 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 a 4-week repeat-dose study in rats comparing Ondibta to US Lantus.

In a 28-day repeat-dose GLP study with a 14-day recovery period Ondibta or US Lantus was given to rats by daily s.c. injection at dose levels of 8.25 or 27.5 U/kg/day which resulted in markedly reduced glucose levels with dose-dependent duration at all dose levels. Three mortalities were noted: one low dose Ondibta rat (toxicokinetic animal) did not recover from anaesthesia after blood collection. Two high-dose Ondibta rats were found dead, one on Day 12 (main study animal) and one on Day 24 (toxicokinetic animal). None of the animals had abnormal gross necropsy findings, and it was considered that they most likely died from exaggerated pharmacology i.e. hypoglycaemia. The NOAEL was 27.5 U/kg/day in animals administered with Ondibta or US Lantus. Findings were comparable whether animals were given Ondibta or US Lantus and were consistent with the pharmacological action of both products. The findings were of small magnitude and had no toxicological relevance. Importantly, considering the human equivalent dose (HED) of the dose levels used in this study (HED 1.33 U/kg for 8.25 U/kg/day; HED 4.44 U/kg for 27.5 U/kg/day, respectively) is much higher than the dose used in Ondibta phase 1 study (0.5 U/kg) and actual dose levels in practice (0.2 U/kg, US Lantus label), the findings observed in this study are likely to be an exaggerated effect of high exposure. Hence, the safety profile of Ondibta and US Lantus was considered comparable in Sprague-Dawley rats.
Of note, when comparing formulations of Ondibta to US Lantus used in the repeat-dose study the certificate of analysis of Ondibta did not specify the content of glycerol but only all other excipients.

Ondibta is considered to be not hazardous to the environment and no special precautions in terms of use and disposal are needed.

2.4.7. Conclusion on the non-clinical aspects

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Ondibta is not expected to pose a risk to the environment.

The *in vitro* pharmacology studies provided adequate evidence of biosimilarity between Ondibta and the EU-approved reference product Lantus with respect to receptor binding affinity, receptor phosphorylation, metabolic activity and mitogenic potential. Additionally, biosimilarity was also seen for *in vitro* IR-B potency.

Based on a 4-week repeat-dose toxicity study in rats the assessment of systemic exposure and the safety profile of insulin glargine for Ondibta and US Lantus at doses of up to 27.5 U/kg/day can be considered comparable. Bioanalytical methods were adequately validated to support the bioanalysis of insulin glargine and anti-insulin glargine antibodies in the 4-week repeat-dose toxicology study in rats. In addition, method validation reports for the conducted *in vitro* pharmacology studies were submitted and assessed as part of the quality dossier and no concerns were identified.

In conclusion, the non-clinical data supported biosimilarity of Ondibta to the EU-approved reference product Lantus. The *in vivo* study showed that Ondibta and US Lantus at doses of up to 27.5 U/kg/day can be considered comparable.

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**

Table 2.7.3- 1 List of all the Clinical Studies

Study/Phase	Objectives	Subject Population	Endpoints	Location of Study Report
Pivotal/PK/PD similarity study (GL-GLA-CT-1002)	To compare the PK and PD profile of GL Glargine Injection with that of US Lantus and EU Lantus	Subjects with T1DM	Primary Pharmacokinetic Endpoints: • $AUC_{ins.0-24h}$ • $C_{ins.max}$ Primary Pharmacodynamic Endpoints: • $AUC_{GIR.0-24h}$ • GIR_{max} Secondary Pharmacokinetic Endpoints: • $AUC_{ins.0-12h}$, $AUC_{ins.12-24h}$, $AUC_{ins.0-\infty}$ • $t_{max.ins}$, Secondary Pharmacodynamic Endpoints: • $AUC_{GIR.0-12h}$ • $AUC_{GIR.12-24h}$ • $AUC_{GIR.0-last}$ • $t_{max.GIR}$	5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports
T1DM/study(GL-GLAT1-3001)	To compare the immunogenicity, efficacy, and safety of GL Glargine Injection with those of EU Lantus	Subjects with T1DM	Primary Endpoint: Immunogenicity: • the percentage of subjects in each treatment group who developed treatment-induced AIA Key Secondary Endpoint: Efficacy: • The change in glycosylated hemoglobin (HbA1c) from baseline at visit Week 26 Other Secondary Endpoints: Immunogenicity: • The percentage of subjects in each treatment group with negative AIA at baseline who developed	5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
			confirmed positive AIA after baseline and up to visit Week 26 • The percentage of subjects in each treatment group with confirmed positive AIA at baseline and at least a 4-fold increase in titers after baseline and up to visit Week 26 • The mean change from baseline in each treatment group in AIA titers after baseline and up to visit Week 26 • The percentage of subjects in each treatment group with confirmed positive AIA after baseline and up to visit Week 26 who developed any anti-insulin NAbs after baseline and up to visit Week 26 • The percentage of subjects in each treatment group with confirmed positive AIA after baseline and up to visit Week 26 Efficacy: • The number and percentage of subjects who achieve a fasting blood glucose (FBG) test result of ≤ 6.0 mmol/L (≤ 108.0 mg/dL) at visit Week 26 • The number and percentage of subjects who achieve a HbA1c of < 7.0% at visit Week 26	
T2DM/study(GL-GLAT2-3002)	To compare the immunogenicity, efficacy, and safety of GL Glargine Injection with those of EU Lantus	Subjects with T2DM	Primary Endpoint: Immunogenicity: • The primary endpoint was the percentage of subjects in each	5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

			treatment group who developed treatment-induced AIA, defined as newly confirmed positive AIA development or important (at least a 4-fold) increase in titers, after baseline and up to visit Week 26 Key Secondary Endpoint: Efficacy: • The change in glycosylated hemoglobin (HbA1c) from baseline at visit Week 26 Other Secondary Endpoints: Immunogenicity: • The percentage of subjects in each treatment group with negative AIA at baseline who developed confirmed positive AIA after baseline and up to visit Week 26 • The percentage of subjects in each treatment group with confirmed positive AIA at baseline and at least a 4-fold increase in titers after baseline and up to visit Week 26 • The mean change from baseline in each treatment group in AIA titers after baseline and up to visit Week 26 • The percentage of subjects in each treatment group with confirmed positive AIA after baseline and up to visit Week 26 who developed any anti-insulin NAbs after baseline and up to visit Week 26 • The percentage of subjects in each treatment group with confirmed	
			positive AIA after baseline and up to visit Week 26 Efficacy: • The number and percentage of subjects who achieved a fasting blood glucose (FBG) test result of ≤ 8.0 mmol/L ≤144.0 mg/dL) at visit Week 26 • The number and percentage of subjects who achieved an HbA1c of <7.0% at visit Week 26	

EU=European Union; GL=Gan & Lee; PD=pharmacodynamics; PK=pharmacokinetics; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; US=United States; AUC= area under curve, $C_{ins.max}$=maximum observed insulin concentration, AUC_{ins} =area under the plasma* insulin concentration curve, $t_{max.ins}$ =time to maximum observed plasma* insulin concentration, GIR=Glucose Infusion Rate, AUC_{GIR} = area under the glucose infusion rate, GIR_{max} = maximum observed glucose infusion rate, $t_{max.ins}$=time to maximum observed plasma* insulin concentration $t_{max.GIR}$ =time to maximum glucose infusion rate, HbA1c=glycosylated hemoglobin, AIA=anti-insulin antibodies, Nabs=neutralizing antibodies, FBG= fasting blood glucose.

Pilot Study (GL-GLA-001)	To compare the PK and PD profile of GL Glargine Injection with that of US Lantus	Subjects with T1DM	5.3.5.4 Other Study Reports

EU=European Union; GL=Gan & Lee; PD=pharmacodynamic; PK=pharmacokinetic; T1DM=type 1 diabetes mellitus; T1DM=type 2 diabetes mellitus; US=United States.

2.5.2. Clinical pharmacology

2.5.2.1. Methods

Bioanalysis. In the clinical studies (GL-GLA-CT-1002 and GL-GLAT1-3001) the analytes insulin glargine, the glargine metabolite M1 and the glargine metabolite M2 were quantified with a validated UPLC-MS/MS method

following Mass Spectrometric Immunoassay (MSIA)extraction and with bovine insulin as the internal standard. The method has been fully validated to quantify insulin glargine, the M1 metabolite and the M2 metabolite in human plasma. The in-study QC samples, the data of back-calculated calibration standards and ISR results demonstrated reliable performance of the bioanalytical methods in the GL-GLA-CT-1002 study and the GL-GLAT1-3001 study.

Anti-insulin antibody (AIA) assay. In the clinical studies the presence of anti-insulin antibody (AIA) was tested with a validated electrochemiluminescence immunoassay method. The AIA method was demonstrated to be sensitive, selective and specific. AIA assay drug tolerance was determined to glargine for the detection of polyclonal anti-glargine antibody. A comparable ability of GL glargine and EU Lantus to inhibit binding of the anti-glargine antibody in the assay was shown.

NAb assay. The AIA positive samples from the clinical study GL-GLAT-3001 and GL-GLAT-3002 were further evaluated in an anti-Glargine Neutralising Antibody assay. The Nab assay is a cellular assay using CHO-K1 IR2 cells overexpressing the insulin receptors 2 (IR2). Glargine activation of IR2 leads to its phosphorylation, which was detected with an ECL immunoassay. The Nab assay was validated according to regulatory guideline with respect to sensitivity, precision, matrix selectivity, drug tolerance, prozone/hook effect, specificity, cross reactivity, biosimilarity, PC and glargine stock solution stability.**3.4.1.2 Study design of pivotal PK/PD similarity study GL-GLA-CT-1002**

The pivotal PK/PD study GL-GLA-CT-1002 was designed to demonstrate PK and PD equivalence of Ondibta with EU Lantus. The study also included US Lantus. This Phase 1 study was a randomised, double-blind, single-dose, 3-way cross-over study was conducted in 114 white male subjects with T1DM. Subjects were randomised to 6 sequences with 3 periods of treatment (6x3) and a washout period between each treatment period, see Figure 9.1 below. In each period of treatment, a single sc. dose of 0.5 U/kg of the respective glargine was administered. In addition to PD clamp measurements, PK-samples for each subject were taken pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 30 hours (hr) post-dose, to provide a full 30 hr plasma PK-profile for glargine, M1 and M2.

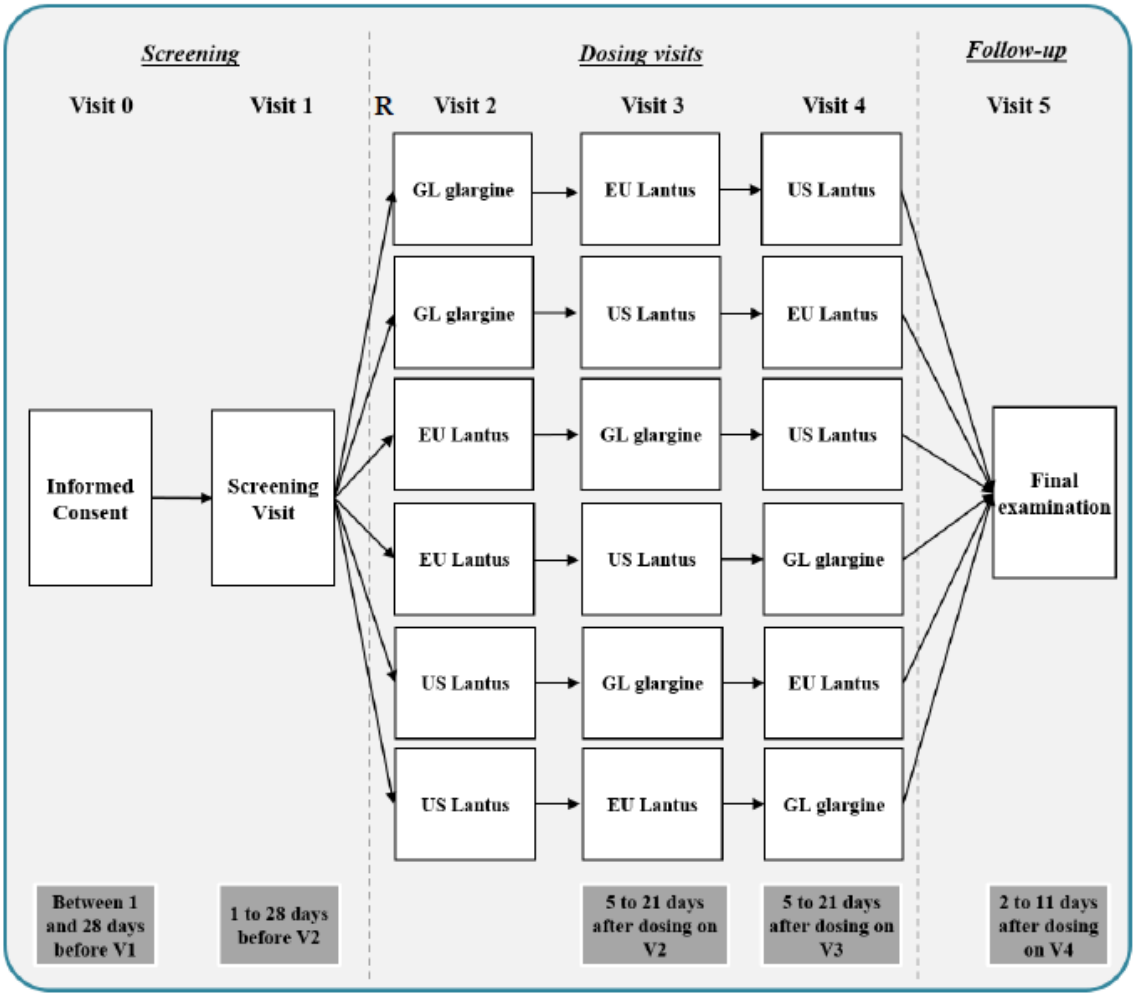


Figure 9-1 Schematic Overview of the Chronological Structure of the Trial

R: Randomization, V: Visit

The **primary objectives** of the study were to

- evaluate biosimilarity with regard to the total and maximum PK exposure during one dosing interval ($AUC_{ins.0-24h}$, $C_{ins.max}$) of Ondibta with Lantus (US RLD/EU RP) in subjects with T1DM.
- evaluate biosimilarity with regard to the total and maximum PD response during one dosing interval ($AUC_{GIR.0-24h}$, GIR_{max}) of Ondibta with Lantus (US RLD/EU RP) in subjects with T1DM.

Pharmacokinetic endpoints

The exposure, AUC_{0-24h} and C_{max}, of the glargine metabolite M1 was chosen as the primary endpoints in the study. Supportive analysis of the primary PK endpoints derived from the insulin glargine as well as from the insulin glargine M2 data were also conducted. Additionally, supportive secondary PK endpoints (AUC_{0-12h}, AUC_{12-24h}, $AUC_{0-\infty}$, t_{max}) were evaluated for M1. The exploratory endpoints $t_{1/2}$ and λ_z for M1 were also included in the analysis.

Secondary pharmacodynamic endpoints

$AUC_{GIR.0\text{-}12h}$, $AUC_{GIR.12\text{-}24h}$, areas under the glucose infusion rate curve in the indicated time-intervals

$AUC_{GIR.0\text{-}last}$, area under the glucose infusion rate curve from 0 hours until the end of clamp

$t_{max.GIR}$, time to maximum glucose infusion rate

Methods

Study population

Inclusion criteria:

A subject was eligible for inclusion in this trial only if all of the following screening criteria were met:

1. Signed and dated informed consent obtained before any trial-related activities

2. Male subject with T1DM for at least 12 months prior to screening as diagnosed clinically

3. Age between 18 and 64 years, both inclusive

4. Body Mass Index (BMI) between 18.5 and 29.0 kg/m2, both inclusive

5. N-(1-deoxy)-fructosyl-haemoglobin (HbA_{1c}) ≤ 9.0 %

6. Fasting negative C-peptide (≤ 0.30 nmol/L)

7. Total insulin dose of < 1.2 (I)U/kg/day

8. Stable insulin regimen for at least 2 months prior to screening

9. Considered generally healthy (apart from T1DM) upon completion of medical history, physical examination, vital signs, ECG and analysis of laboratory safety variables, as judged by the investigator.

Exclusion criteria:

A subject was not eligible for inclusion in this trial if any of the following criteria were met at screening:

1. Known or suspected hypersensitivity to IMPs or related products.

2. Previous participation in the trial (defined as randomised).

3. Receipt of any medicinal product in clinical development within 30 days or 5 half-lives (whichever is longer) before randomisation in this trial.

4. History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction.

5. Any history or presence of cancer except basal cell skin cancer or squamous cell skin cancer as judged by the investigator.

6. Any history or presence of clinically relevant comorbidity (with the exception of conditions associated with diabetes mellitus), or signs of acute illness, as judged by the investigator.

7. Proliferative retinopathy or maculopathy (based on a recent [<1.5 years] ophthalmologic examination) and/or severe neuropathy, in particular autonomic neuropathy, as judged by the investigator.

8. Recurrent severe hypoglycaemia (more than 1 severe hypoglycaemic event during the past 6 months) or hypoglycaemic unawareness as judged by the investigator.

9. Increased risk of thrombosis, e.g. subjects with a history of deep leg vein thrombosis or family history of deep leg vein thrombosis, as judged by the investigator.

10. Significant history of alcoholism or drug abuse as judged by the investigator or consuming more than 24 g alcohol/day.

11. Symptomatic hypotension or supine blood pressure at screening (after resting for at least 5 min in supine position) outside the range of 90-140 mmHg for systolic or greater than 90 mmHg for diastolic pressure.

Clarification regarding exclusion criterion 11: Excluding white-coat hypertension. If a repeated measurement showed values within the range, the subject could be included in the trial. This exclusion criterion also pertained to subjects being on anti-hypertensives.

12. Heart rate at rest outside the range of 50-90 beats per minute.

13. Clinically significant abnormal standard 12-lead ECG after 5 minutes resting in supine position at screening, as judged by the investigator.

14. A positive result in the alcohol and/or urine drug screen at the screening visit.

15. Not able or willing to refrain from smoking and use of nicotine substitute products one day before and during the inpatient period.

16. Positive to the screening test for Hepatitis Bs antigen or Hepatitis C antibodies and/or a positive result to the test for HIV-1/2 antibodies or HIV-1 antigen.

17. Any medication (prescription and non-prescription drugs) within 14 days before IMP administration, with the exception of occasional use of paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs).

Clarification regarding exclusion criterion 17: Exceptions were insulin products, stable treatment with thyroid hormones, lipid-lowering and/or antihypertensive drugs. Paracetamol or NSAIDs for occasional use to treat pain were allowed.

18. Blood donation or blood loss of more than 500 mL within the last 3 months.

19. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

20. Fertile male with female partner(s) without using a highly effective contraceptive method in combination with spermicide-coated condoms from the first dosing until 1 month after dosing.

Clarification regarding exclusion criteria 20: Highly effective contraceptive methods were considered those with a failure rate less than 1% undesired pregnancies per year including surgical sterilisation, hormonal intrauterine devices (coil), oral hormonal contraceptives, sexual abstinence or a surgically sterilised partner. Surgically sterilised men were considered as not being fertile.

Statistics

For similarity analysis of the primary PK endpoints, $AUC_{ins.0\text{-}24h}$ and $C_{ins.max}$, derived from the insulin glargine M1 data were logarithmically transformed as a log-normal distribution was assumed. The logarithm-transformed endpoints were analysed using analysis of variance (ANOVA) with clinical site, sequence, subject within sequence, period, and insulin formulation as fixed effects.

For analysis of the primary PD endpoints, $AUC_{GIR.0-24h}$ and GIR_{max} data were not logarithmically transformed as normal distribution was assumed. The main analysis based on untransformed endpoints was analysed using ANOVA with clinical site (only if significant), sequence, subject within sequence, period, and insulin formulation as fixed effects.

In addition to the primary analysis, a supportive analysis and a sensitivity analysis were performed.

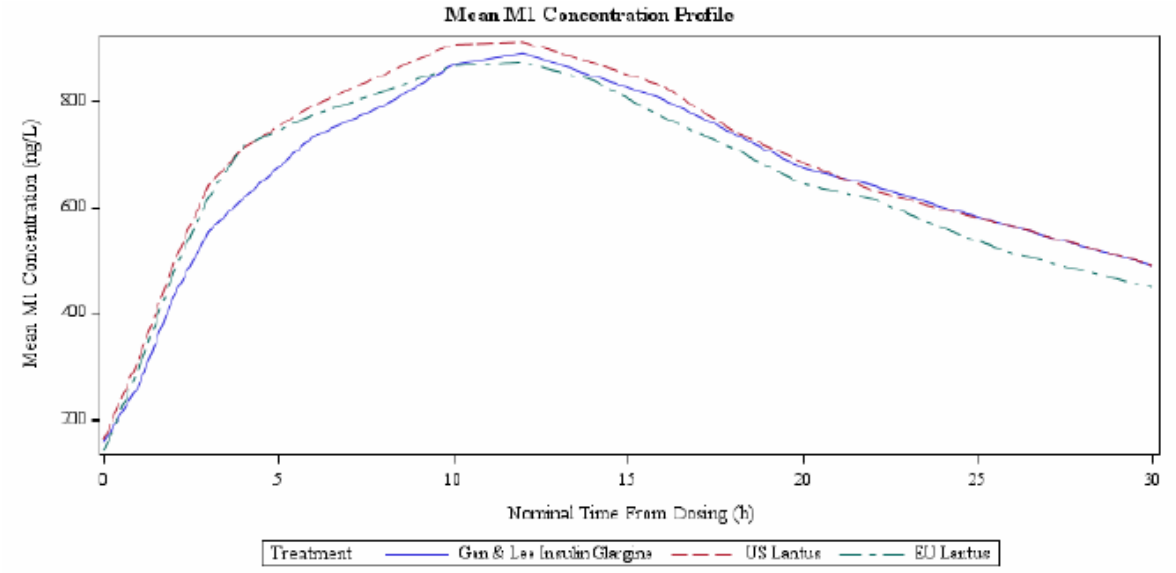
2.5.2.2. A post-hoc analysis providing descriptive statistics of primary PK and PD endpoints based on anti-insulin antibody status (positive/negative) was conducted in order to determine if anti-insulin antibody status had an impact on the primary endpoints. PD statistical analyses were conducted for the per protocol set (PPS, N=110), which included all randomised subjects who completed the trial without any important protocol deviation. Pharmacokinetics

PK-endpoint analysis in PK/PD similarity study GL-GLA-CT-1002

A total of 114 subjects were randomised to one of the treatment sequences and are included in the full analysis set (FAS) and analysis of PK endpoints was performed on the per-protocol-set (PPS) set that consisted of all 110 completers of the trial. In the comparability analysis of PK-endpoints further subjects were excluded from the PPS for descriptive statistics of primary PK endpoints as per pre-defined rules (baseline concentrations were >5% of $C_{ins.max}$ or PK measurement of the clamp ended before 24 h).

The mean insulin glargine M1 concentration profiles of Ondibta, US Lantus, and EU Lantus were compared by overlaying the profiles, see Figure 2.7.1-1 below.

Figure 2.7.1- 1: Mean Plasma Insulin Glargine M1 Profiles after s.c. Administration of 0.5 U/kg GL Glargine, US Lantus, and EU Latus, Linear Scale (PPS)



Source: Study GL-GLA-CT1002 CSR Figure 11-1

Descriptive statistics of the NCA determined primary and secondary PK endpoints was done by treatment and the results of the main statistical analysis for insulin glargine M1 are presented in table 2.5-2 below.

Table 2.5- 2: Descriptive Statistics of the Primary and Secondary Pharmacokinetic Endpoints for Insulin Glargine M1

Parameter	Treatment	N	Arithmetic mean	SD	%CV	Min	Median	Max	Geometric Mean
$AUC_{ins.0-24h}$ [h*ng/L]	GL Glargine	101	16977.3	16419.80	96.7	5674	12757.8	133366	13939.9
	US Lantus	98	17625.1	18818.27	106.8	5598	13016.5	147105	14113.5
	EU Lantus	100	17010.9	18330.50	107.8	3955	12853.3	156950	13627.5
$C_{ins.max}$[ng/L]	GL Glargine	101	972.5	952.65	98.0	359	721.0	7810	796.5
	US Latus	98	1001.9	1052.49	105.1	339	738.5	8180	804.2
	EU Lantus	100	979.2	1060.21	108.3	271	743.5	9180	783.4
$AUC_{ins.0-12h}$ [h*ng/L]	GL Glargine	101	7935.1	7268.83	91.6	2802	5920.0	60806	6620.7
	US Lantus	98	8535.1	8580.61	100.5	2631	6408.0	68225	6929.6
	EU Lantus	100	8319.8	8759.45	105.3	2044	6331.7	73970	6686.3
$AUC_{ins.12-24h}$ [h*ng/L]	GL Glargine	101	9042.2	9219.03	102.0	2563	6582.0	72560	7271.5
	US Lantus	98	9090.1	10329.05	113.6	2784	6489.6	78880	7116.3
	EU Lantus	100	8691.1	9641.81	110.9	1911	6328.9	82980	6887.0
$AUC_{ins.0-\infty}$ (h*ng/L)	GL Glargine	44	36647.4	42087.89	114.8	10109	24570.8	244494	27050.4
	US Lantus	53	32162.0	41537.74	129.2	10157	22250.1	298320	24776.9
	EU Lantus	48	31256.9	25812.21	82.6	7431	24105.8	159924	25853.6
$t_{max.ins}$(h)	GL Glargine	101	11.5	3.36	29.2	3	12.0	24	11.0
	US Lantus	98	10.9	4.23	38.8	1	10.0	24	9.9
	EU Lantus	100	10.8	3.83	35.4	3	12.0	20	10.0

SD: Standard deviation; Min: Minimum; Max: Maximum; $AUC_{ins.0-24h}$: area under the plasma insulin concentration curve from 0 to 24 hours; $C_{ins.max}$: maximum observed insulin concentration; $AUC_{ins.0-12h}$, $AUC_{ins.12-24h}$, $AUC_{ins.0-\infty}$: areas under the plasma* insulin concentration curve in the indicated time intervals; $t_{max.ins}$: time to maximum observed plasma insulin concentration

The following table 2.5-3 displays the main (primary) statistical analysis for treatment comparisons of the primary exposure endpoints of insulin glargine M1.

Table 2.5- 3: Treatment Comparisons of the Primary Pharmacokinetic Endpoints for Insulin Glargine M1

Parameter	Comparison	N	Geometric LS-mean Ratio%	90%CI
$AUC_{ins.0-24h}$ [h*ng/L]	GL glargine vs US Lantus	95	98.36	(93.71; 103.25)
	GL glargine vs EU Lantus	95	102.45	(97.52; 107.62)
$C_{ins.max[ng/L]}$	GL glargine vs US Lantus	95	98.58	(93.38; 104.06)
	GL glargine vs EU Lantus	95	101.52	(96.04; 107.31)

Geometric LS-mean ratio: Exponentiated least-square mean ratio, CI: Confidence interval.
Logarithm-transformed endpoints were analyzed using analysis of variance (ANOVA) for obtaining LS-mean ratio and 90 Cis.

In the statistical analysis, the 90% CIs of $AUC_{ins.0-24h}$ and $C_{ins.max}$ estimated ratio derived from the insulin glargine M1 data for Ondibta vs EU Lantus fell within the BE limits of 80% to 125%, the criteria for defining PK biosimilarity. The results obtained therefore demonstrate PK biosimilarity between Ondibta and EU Lantus for the primary PK endpoints. The supportive endpoints based on insulin glargine and M2 was supportive, see table 2.7.1.-6. The secondary and exploratory PK endpoints were also supportive for the conclusion of biosimilarity, see Table 2.7.1-9.

Table 2.7.1- 6: **Treatment Comparison of Primary Pharmacokinetic Endpoints for Glargine and Insulin Glargine M2 vs. EU Lantus**

Parameter	Analysis/ Transformation	N	Treatment/Comparison	LS-Mean	Ratio of LS-Means	90% CI of the Ratio
Glargine						
$AUC_{ins.0-24}$ (h*ng/L)	Supportive analysis	58	Gan & Lee Insulin Glargine	3860.0	105.34	(99.96; 111.00)
		58	EU Lantus	3664.4		
$C_{ins.max}$ (ng/L)	Supportive analysis	92	Gan & Lee Insulin Glargine	205.08	98.40	(93.38; 103.69)
		92	EU Lantus	208.41		
Insulin Glargine M2						
$AUC_{ins.0-24}$ (h*ng/L)	Supportive analysis	24	Gan & Lee Insulin Glargine	3627.5	99.50	(85.41; 115.91)
		24	EU Lantus	3645.9		
$C_{ins.max}$ (ng/L)	Supportive analysis	25	Gan & Lee Insulin Glargine	308.95	100.40	(85.67; 117.67)
		25	EU Lantus	307.71		

Table 2.7.1-9: **Treatment Comparison of Secondary PK Endpoints for GL Glargine Injection vs EU Lantus**

Parameter	Treatment/Comparison	N	LS-Mean/LS Mean Ratio	90% CI
$AUC_{ins.0-12}$ (h*ng/L)	GL Glargine Injection	95	6728.8	
	EU Lantus	95	6806.2	
	GL Glargine Injection vs EU Lantus	.	98.83	93.64; 104.32
$AUC_{ins.12-24}$ (h*ng/L)	GL Glargine Injection	95	7435.1	
	EU Lantus	95	7008.8	
	GL Glargine Injection vs EU Lantus	.	106.08	101.11; 111.30
$AUC_{ins.0-\infty}$ (h*ng/L)	GL Glargine Injection	25	28215	
	EU Lantus	25	25374	
	GL Glargine Injection vs EU Lantus	.	111.20	100.88; 122.58

Post-hoc analysis of PK Endpoints in GL-GLA-CT-1002 study – Impact of anti-insulin antibody status

In a post-hoc analysis of the primary PK endpoints in the pivotal GL-GLA-CT-1002 study it was shown that the mean $AUC_{ins,0-24hr}$ and $C_{ins,max}$ in AIA positive subjects were approximately 2-3-fold higher than in AIA negative subjects, see table 11-7 below.

Table 11-7 Descriptive Statistics of the Primary Pharmacokinetic Endpoints for Insulin Glargine M1 by Anti-Insulin Antibody Status (PPS), Post-hoc Analysis

			Parameter Statistic					
Parameter	Treatment	ADA Status	N	Arithmetic Mean	SD	Min	Median	Max
$AUC_{ins.0-24h}$ (h*ng/L)	GL glargine	Negative	72	12304.7	4401.42	6549	11428.8	34481
	GL glargine	Positive	29	28578.4	26799.87	5674	18918.0	133366
	US Lantus	Negative	71	12297.7	4799.64	5598	11857.1	40300
	US Lantus	Positive	27	31634.3	31270.36	7977	19864.0	147105
	EU Lantus	Negative	72	11875.6	4648.20	3955	11874.1	36359
	EU Lantus	Positive	28	30215.8	30398.34	8119	17893.5	156950
$C_{ins.max}$ (ng/L)	GL glargine	Negative	72	710.6	268.38	359	640.0	1870
	GL glargine	Positive	29	1622.9	1563.36	373	1000.0	7810
	US Lantus	Negative	71	709.0	282.28	339	665.0	2150
	US Lantus	Positive	27	1772.1	1751.50	457	1210.0	8180
	EU Lantus	Negative	72	692.8	278.04	271	683.5	2060
	EU Lantus	Positive	28	1715.6	1771.19	425	1015.0	9180

ADA: Anti-drug antibody (anti-insulin antibody)
Cross reference: EOT Table 14.4.7.5

Pharmacokinetic data in clinical study GL-GLAT-3001

Study GL-GLAT1-3001 was conducted to compare the immunogenicity, safety, and efficacy of Ondibta with that of the reference medicinal product, EU Lantus, in adults (18 through 75 years of age) with T1DM. PK-

samples of a sub-set of included subjects (N=93 glargine group, N=106 lantus group) were collected at Day 1 and weeks 2, 4, 8, 12, 16, 20, and 26 for concentration-response analysis to examine the relationship between the plasma concentrations of insulin glargine, M1, and M2, and immunogenic response. The mean plasma concentration of the relevant metabolite M1 was compared between the Ondibta and EU Lantus group. See table 2.7.1.-20 below.

Table 2.7.1- 20: Summary of M1 Plasma Concentration (pg/mL) by Time Point (PK Analysis Set)

Time points	GL Glargine (N=93)			Lantus (N=106)		
	n	Mean (SD)	Geometric mean	n	Mean (SD)	Geometric mean
Baseline	63	263.46 (288.450)	361.8	73	306.60 (361.140)	370.4
Week 2	66	496.29 (438.020)	428.2	74	514.48 (398.930)	442.7
Week 4	66	468.21 (411.680)	412.4	73	520.05 (433.178)	432.2
Week 8	66	467.89 (638.740)	388.4	81	612.20 (1100.564)	433.0
Week 12	71	501.54 (768.501)	403.3	83	603.76 (984.353)	437.7
Week 16	76	485.43 (711.563)	397.9	88	603.04 (1037.306)	411.8
Week 20	78	514.99 (888.831)	405.1	85	618.31 (1091.839)	428.0
Week 26	84	467.71 (624.424)	374.9	88	432.97 (413.469)	334.6
EOT	89	463.87 (607.209)	375.3	91	425.33 (409.667)	333.5

Source: Study GL-GLAT1-3001 CSR Table 14.3.6.1.2

2.5.2.3. Pharmacodynamics

Mechanism of action

The active substance in Ondibta is insulin glargine, a slow-acting insulin analogue. As with all insulins, insulin glargine exerts its pharmacodynamic effects through binding to the insulin receptor at target tissues including liver, skeletal muscle, and adipose tissue.

Primary and Secondary pharmacology

The pharmacodynamics (PD) of Ondibta was evaluated in Study 1002. The primary PD objective of the study was to evaluate biosimilarity with regard to the total and maximum PD response during one dosing interval ($AUC_{GIR.0-24h}$, GIR_{max}) of Ondibta with Lantus (US RLD/EU RP) in subjects with T1DM.

PD endpoints were derived from glucose infusion rates (GIR) measured by the euglycemic glucose clamp device (Clam part) over the 30-hour sampling period. The euglycemic glucose clamp is a validated method in which the GIR needed to ensure a constant blood glucose at a pre-determined level is used as a surrogate marker for the PD effect of a glucose-lowering drug. During the entire glucose clamp period, a target blood glucose level of 100 mg/dL was strived for. The clamp setting was based on an automated glucose clamp technique with continuous blood glucose measurements and minute-by-minute adaptations of glucose infusion rates to achieve the highest clamp quality possible while also reducing potential investigator-related bias. Moreover, the euglycemic clamp technique minimised the risk of any drug-induced hypoglycaemia.

PD Results:

In total, 114 subjects (62 at trial site Profil Neuss and 52 at trial site Profil Mainz) were randomised to one of the treatment sequences.

Figure 11-2 shows the overlaid mean smoothed GIR profiles of Ondibta, US Lantus, and EU Lantus. The mean plot of smoothed data is based on all dosed subjects, i. e. 110 subjects for Ondibta, 111 subjects for US Lantus, and 112 subjects for EU Lantus.

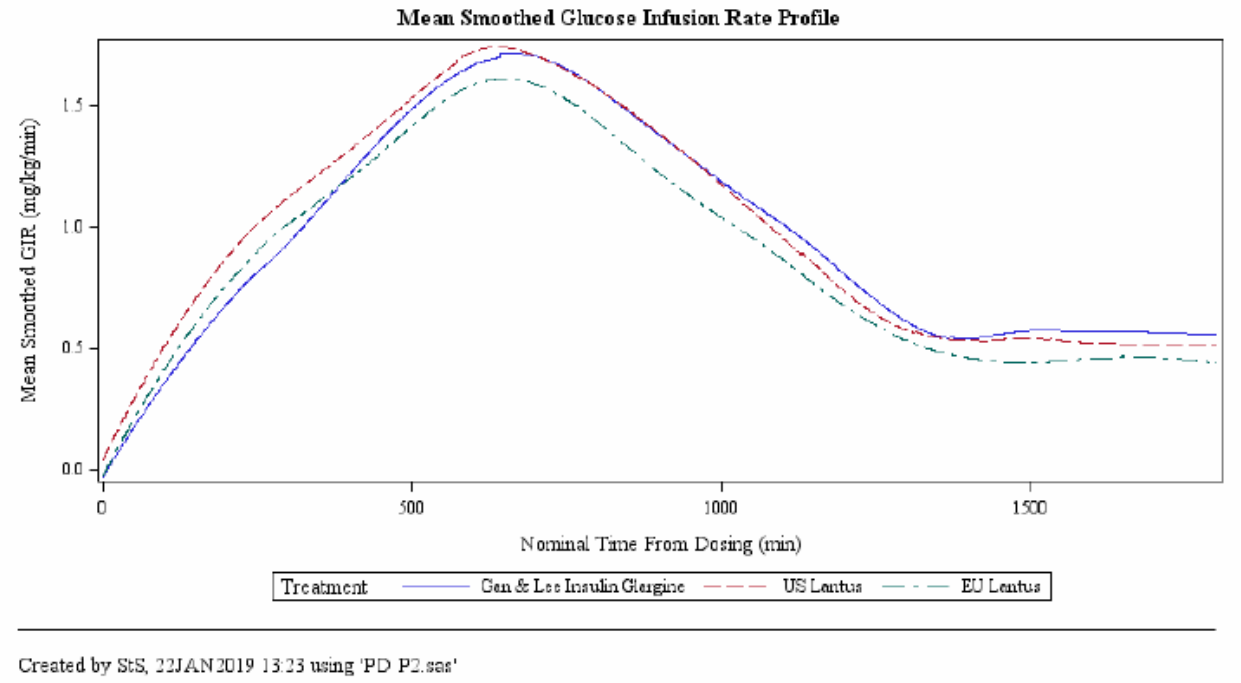


Figure 11-2 Mean of Smoothed GIR Profiles after s.c. Administration of 0.5 U/kg GL Glargine, US Lantus, and EU Lantus, Linear Scale (PPS)

Cross reference: EOT Figure 14.2.16.4

A descriptive statistics overview of the primary PD endpoints by treatment are presented in **Table 11-8**.

Table 11-8 Descriptive Statistics of Primary Pharmacodynamic Endpoints (PPS)

Lab Parameter	Treatment	N	Arithmetic Mean	SD	CV%	Min	Median	Max
$AUC_{GIR,0-24h}$ (mg/kg)	GL glargine	109	1524.6	1043.53	68.4	0	1324.5	6087
	US Lantus	109	1584.3	961.31	60.7	0	1551.9	4785
	EU Lantus	109	1426.2	1035.67	72.6	0	1128.8	5708
GIR_{max} (mg/kg/min)	GL glargine	109	1.920	1.2204	63.6	0.00	1.608	9.00
	US Lantus	109	2.008	1.1930	59.4	0.00	1.819	7.44
	EU Lantus	109	1.789	1.1460	64.1	0.00	1.438	6.46

Cross reference: EOT Table 14.2.9

Analysis of Primary Pharmacodynamic Endpoints: Treatment Comparison of Ondibta and EU Lantus RP

Main (primary), supportive, and sensitivity analysis results of primary PD endpoints for Ondibta vs. EU Lantus are shown in **Table 11-10**.

Table 11-10 Treatment Comparison of the Primary Pharmacodynamic Endpoints, GL Glargine vs. EU Lantus (PPS)

			LS-Means [1]					
Endpoint	Analysis [2]/ Transformation	N	GL glargine	EU Lantus	Ratio of LS Means [3]	95% CI of the Ratio [4]	Guideline for Equivalence Limits (%)	CI Contained within Guideline
$AUC_{GIR.0-24h}$ (mg/kg)	Main (Primary) (Untransformed) [5]	108	1530.5	1435.4	106.63	(96.24; 118.35)	(80.00, 120.00)	Yes
	Supportive (Log-transformed) [6]	108	1124.3	995.17	112.98	(94.77; 134.68)	(80.00, 125.00)	No
	Sensitivity (Log-transformed) [7]	102	1254.8	1212.9	103.45	(91.55; 116.91)	(80.00, 125.00)	Yes
GIR_{max} (mg/kg/min)	Main (Primary) (Untransformed) [5]	108	1.93	1.80	107.17	(96.00; 119.68)	(80.00, 120.00)	Yes
	Supportive (Log-transformed) [6]	108	1.57	1.42	110.47	(95.60; 127.67)	(80.00, 125.00)	No
	Sensitivity (Log-transformed) [7]	102	1.71	1.63	104.93	(95.14; 115.72)	(80.00, 125.00)	Yes

Note 1: The Least Squares (LS) Means reported here for the main analysis were arithmetic LS-means. LS-means reported here for the supportive and sensitivity analyses for which the model was fit to the log-transformed data, were back transformed from the ANOVA parameter estimates by exponentiation.
Note 2: Profiles excluded from this analysis are flagged with their reason in Appendix 16.2.3.2
Note 3: Ratio of the LS Means are the GL glargine over EU Lantus multiplied by 100.
Note 4: CI: Confidence Intervals for the ratios. For the main analysis, CIs were determined according to Fieller's Theorem. For the supportive and sensitivity analyses for which the model was fit to the log-transformed data, were back-transformed from the ANOVA CI limits by exponentiation.
Note 5: Primary Analysis EOT Table 14.2.11.1 and program source PDPA1.sas.
Note 6: Supportive Analysis EOT Table 14.2.11.2 and program source PDPA2.sas.
Note 7: Sensitivity Analysis EOT Table 14.2.11.3 and program source PDPA3.sas.
Cross reference: EOT Table 14.2.11.1, EOT Table 14.2.11.2, EOT Table 14.2.11.3

The results of the statistical analysis demonstrate that for both primary PD endpoints $AUC_{GIR.0-24h}$ and GIR_{max} the similarity limits (95% CI of the LS-mean ratio of untransformed data of treatments within the limits 80.00-120.00%) were met. Thus, PD similarity of Ondibta and EU Lantus was demonstrated.

For the sensitivity analysis, low responders (Subjects 111, 124, 147, 208, and 271) were further excluded from the analysis set used for main (primary) analysis due to lack or very low PD response for the reference (i.e. EU Lantus) treatment.

Analysis of Secondary Pharmacodynamic Endpoints: Treatment Comparison of Ondibta and EU Lantus

Statistical analysis results of secondary PD endpoints for treatment comparison of Ondibta and EU Lantus are presented in **Table 14.2.14.1** and the nonparametric analysis of $t_{max.GIR}$ is presented in **Table 14.2.14.2**. The results of the statistical analysis demonstrate that for the secondary AUC_{GIR} endpoints ($AUC_{GIR.0-12h}$ and $AUC_{GIR.0-last}$) the similarity limits (95% CI of the estimated LS-mean treatment ratio of untransformed data within the limits 80.00–120.00%) were met for Ondibta and EU Lantus.

To analyse $t_{max.GIR}$ nonparametric methods were used. There was no statistically significant difference in $t_{max.GIR}$ between Ondibta and EU Lantus (p=0.2000).

14.2.14.1 Fieller Analysis of the Secondary Pharmacodynamic Endpoints

Fieller Analysis of Gan & Lee Insulin Glargine vs. EU Lantus (Secondary PD Endpoints)
Per Protocol Population

Parameter	Treatment/Comparison	N	LS-Mean/ LS-Mean Ratio	95%-CI (1)	Site Effect Significant?
AUC-GIR 0-12h (mg/kg)	Gan & Lee Insulin Glargine	108	771.27		
	EU Lantus	108	764.23		
	Gan & Lee Insulin Glargine vs EU Lantus	.	100.92	(89.87;113.31)	No
AUC-GIR 12-24h (mg/kg)	Gan & Lee Insulin Glargine	108	759.22		
	EU Lantus	108	671.16		
	Gan & Lee Insulin Glargine vs EU Lantus	.	113.12	(101.69;126.28)	No
AUC-GIR 0h-last (mg/kg)	Gan & Lee Insulin Glargine	107	1735.7		
	EU Lantus	107	1599.1		
	Gan & Lee Insulin Glargine vs EU Lantus	.	108.54	(98.57;119.76)	No

14.2.14.2 Non-parametric Analysis of the Secondary Pharmacodynamic Endpoint t_{GIRmax}

Nonparametric Analysis of Gan & Lee Insulin Glargine vs. EU Lantus (Secondary PD Endpoints)
Per Protocol Population

Parameter	Treatment/Comparison	N	Median/ Estimate of Hodges and Lehmann	95%-CI (1)	p-Value
Time until GIRmax (h)	Gan & Lee Insulin Glargine	104	11.083		.
	EU Lantus	104	10.667		.
	Gan & Lee Insulin Glargine vs EU Lantus	.	0.417	(-0.2500; 1.0667)	0.2000

Post-hoc Analysis of Pharmacodynamic Endpoints – Impact of Anti-Insulin Antibody Status

A single sample for determination of anti-insulin antibody was taken pre-dose at Visit 2 (baseline). The presence of anti-insulin antibodies was investigated in all subjects of the safety analysis set (except for Subjects 108 and 245 who had withdrawn their consent). At visit 2, 30 of 112 subjects had confirmed positive anti-insulin antibody prior to the first dosing.

A post-hoc analysis, presented in **Table 11-13**, was made to determine if anti-insulin antibody status (positive/negative) had an impact on PD endpoints.

Table 11-13 Descriptive Statistics of the Primary Pharmacodynamic Endpoints by Anti-Insulin Antibody Status (PPS), Post-hoc Analysis

			Parameter Statistic					
Parameter	**Treatment**	**ADA Status**	**N**	**Arithmetic Mean**	**SD**	**Min**	**Median**	**Max**
$AUC_{GIR.0-24h}$ (mg/kg)	GL glargine	Negative	80	1495.824	1108.570	0.00	1256.307	6087.16
	GL glargine	Positive	29	1604.013	850.8774	50.83	1597.925	3280.85
	US Lantus	Negative	79	1498.015	899.1484	0.00	1437.965	4785.05
	US Lantus	Positive	30	1811.389	1092.425	76.14	1831.787	4466.64
	EU Lantus	Negative	80	1366.003	1062.153	0.00	1061.805	5707.67
	EU Lantus	Positive	29	1592.352	956.6666	138.58	1181.140	3233.86
GIR_{max} (mg/kg/min)	GL glargine	Negative	80	1.911	1.3356	0.00	1.545	9.00
	GL glargine	Positive	29	1.945	0.8436	0.36	1.939	3.68
	US Lantus	Negative	79	1.953	1.2092	0.00	1.789	7.44
	US Lantus	Positive	30	2.153	1.1565	0.41	2.087	6.08
	EU Lantus	Negative	80	1.755	1.2321	0.00	1.382	6.46
	EU Lantus	Positive	29	1.883	0.8775	0.40	1.714	3.62

ADA: anti-drug antibody (anti-insulin antibody)
Cross reference: EOT Table 14.4.7.6

Evidently, in subjects with positive anti-insulin antibody status, a positive pre-existing anti-insulin antibody status did not have a major impact on primary PD analysis. While $AUC_{GIR.0-24h}$ was slightly higher in subjects with positive anti-insulin antibodies, these differences were small in view of the rather large inter-individual differences (indicated by large standard deviations). The mean differences in GIR_{max} were very small between subjects with positive and negative antibodies (below 0.2 mg/kg/min for all treatments) supporting the notion that antibodies had no relevant impact on PD outcomes.

Quality of clamps

The clamp quality parameters precision (in terms of coefficient of variation, or CV[%]) and deviation from target were calculated based on all measurements during the 30-hour clamp procedure where GIR was >0 mg/kg/min as pre-defined in the SAP.

An overview of clamp quality is displayed in **Table 11-14**.

Table 11-14 Descriptive statistics for Quality of Clamp Data (PPS)

Parameter	Treatment	N	Mean	SD	Min	Median	Max
Precision (CV, %)	GL glargine	107	3.92	1.824	1.2	3.45	11.6
	US Lantus	108	4.19	1.769	1.6	3.77	11.1
	EU Lantus	108	3.95	1.668	1.4	3.44	11.4
Deviation from Target (mg/dL)	GL glargine	107	1.08	1.995	-0.2	0.28	13.6
	US Lantus	108	1.09	1.735	-0.2	0.47	12.5
	EU Lantus	108	0.98	1.275	-0.4	0.48	7.3

Cross-reference: EOT Table 14.4.1.1

All subjects met the precision requirement (CV% <15%) and all but 2 subjects met the deviation from target requirement (deviation from target <10 mg/dL).

2.5.3. Discussion on clinical pharmacology

The Applicant Gan & Lee Pharmaceuticals Europe GmbH applied for a marketing authorisation (MA) of Ondibta (insulin glargine). Ondibta for subcutaneous injection is a biosimilar product to the original insulin glargine product Lantus.

The application is supported by 3 clinical studies; one pivotal PK/PD comparability study (GL GLA-CT-1002) and two phase 3 supportive immunogenicity studies, GL GLAT1-3001 and GL GLAT2-3002. The clinical studies were performed in patients with type 1 or type 2 diabetes. The drug products (in a 3.0-mL pre-filled glass cartridge) was assembled in a disposable pen that were used in all the clinical studies.

In the clinical studies (GL-GLA-CT-1002 and GL-GLAT1-3001) the analytes insulin glargine, metabolite M1 and metabolite M2 were quantified with a validated MSIA UPLC-MS/MS method with bovine insulin as the internal standard. From investigation of ADA interference in the BA method, in addition to an ADA stratified analysis of IS data, there was no apparent impact of AIAs on the quantification of M1. Overall, the conducted bioanalysis was found to be in accordance with regulatory requirements.

In the clinical studies the presence of anti-insulin antibody (AIA) was tested with a validated electrochemiluminescence immunoassay method. The AIA method was demonstrated to be sensitive, selective and specific with a sufficient sensitivity and drug tolerance of 160 µg/mL (Glargine M1 C_{max} ~ 1 ng/mL). The AIA positive samples from the clinical study GL-GLAT-3001 and GL-GLAT-3002 were further evaluated in an anti-Glargine Neutralizing Antibody assay. The NAb assay is a cellular based assay. The NAb assay was validated according to regulatory guidelines.

The pivotal PK/PD study GL-GLA-CT-1002 was designed to demonstrate PK and PD equivalence of Ondibta with EU Lantus. The pivotal PK/PD comparability study of Ondibta with EU Lantus was done using the euglycemic clamp technique as recommended in the EMA guideline on insulin biosimilar products: Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (referred to as insulin biosimilar guideline). The Phase 1 GL-GLA-CT-1002 study was a randomized, double-blind, single-dose, 3-way cross-over study was conducted in 114 male subjects with T1DM. PK-samples were taken to provide a full 30 hr plasma PK-profile for glargine, M1 and M2. The sampling period and selected dosage of glargine 0.5 U/kg follows the recommendation in the biosimilar insulin guideline for a long-acting insulin of minimum 24 hr and a dose between 0.4 and 0.6 U/kg.

The exposure, $AUC_{0\text{-}24h}$ and C_{max}, of the glargine metabolite M1 was chosen as the primary endpoints in the study for the three insulin glargines. The selected primary and secondary PK endpoints is in line with the recommendation in the biosimilar insulin guideline. Selection of the predominant active M1 metabolite for primary endpoint is in line with other glargine biosimilar products and the SmPC of Lantus. The selected primary and secondary PK endpoints is in line with the recommendation in the biosimilar insulin guideline.

PK endpoints were determined for 110 subjects. In the biosimilar assessment 14 subjects were exclude due to baseline M1 plasma conc. above 5% of C_{max}. This exclusion criteria are in accordance with the EMA's bioequivalence guideline, though for most subjects the 5% C_{max}, M1 exclusion criteria could not be adequately applied as the 5% C_{max}, M1 value was below the LLOQ (70 ng/L, corresponds to approx. 7% of C_{max}) of the bioanalytical methods. As the BBLQ is close to the 5% BE criteria it is judged not to impact the PK-biosimilarity evaluation. Furthermore, the conclusion of biosimilarity was demonstrated not to be sensitive to exclusion of the 14 subjects.

It was demonstrated by statistical analysis, ANOVA, that for both primary PK endpoints $AUC_{0\text{-}24h}$ and C_{max} of the insulin glargine M1 the similarity limits (90% CI of the geometric LS-mean treatment ratio within the limits 80.00–125.00%) were met. The demonstration of PK-similarity by application of the conventionally bioequivalence acceptance criteria follows the guidelines recommendation. Also, supportive endpoint based on parent, M2, and secondary PK endpoint were supportive for the conclusion of PK-similarity. The US Lantus data were appropriately excluded in the BE ANOVA analysis.

In a post-hoc analysis of the pivotal GL-GLA-CT-1002 study it was shown that the mean $AUC_{0\text{-}24hr}$ and C_{max} in AIA positive subjects were approximately 2-3-fold higher than in AIA negative subjects. The higher exposure of insulin glargine due to AIAs is likely an *in vivo* effect and not an artefact of the BA method. A complementary post-hoc analysis of PK-data from pivotal GL-GLA-CT-1002 study demonstrated that the magnitude of the systemic exposure is of the same order with all the investigational product (Test or References) in subjects with the same ADA status. The confidence intervals for AUC M1,0-24 and M1max in each ADA status group are within the acceptance range for BE. In conclusion, the impact of AIAs on PK had no impact on the conclusion of biosimilarity.

The clinical study GL-GLAT1-3001 was conducted to compare the immunogenicity, safety, and efficacy of Ondibta vs Lantus. Supportive PK data demonstrates that the mean plasma concentrations of M1-glargine in the Ondibta and EU Lantus group are comparable over 26 weeks of treatment.

Pharmacodynamics

The pharmacodynamics (PD) of Ondibta was evaluated in a pivotal randomised, double-blind, single-dose, 3-way cross-over study (GL-GLA-CT-1002) in subjects with T1DM that compared PK/PD of Ondibta to US Lantus and EU Lantus.

The chosen dose of 0.5 U/kg in study 1002 is within the range used in similar glucose clamp studies and in agreement with the EMA guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1). With a high precision (CV% of approximately 4) and a mean deviation from target blood glucose of less than 10%, the clamp studies were comparable among the tested IMPs and of high quality.

The primary PD endpoints, $AUC_{GIR.0\text{-}24h}$ and GIR_{max}, were analysed using untransformed data for the main analysis. The similarity limits (a 95% CI of the LS-mean treatment ratio within the limits of 80.00–120.00%) were met for the primary endpoints when comparing Ondibta to EU Lantus. Two out of three of the secondary PD endpoints were also within the 80-120% BE margin.

As for the impact of anti-insulin antibodies (ADA), the Applicant conducted a post-hoc analysis. This analysis showed no significant effect of ADA on the primary PD endpoints. Approximately 27% of the participants in study 1002 had ADAs. In Study 3001, 12-19% of ADA-positive subjects were found to have neutralising antibodies but a dedicated evaluation of the impact of these NAbs was not performed.

2.5.4. Conclusions on clinical pharmacology

The Applicant conducted three clinical studies to demonstrate that Ondibta has a comparable PK and PD profiles with the reference insulin glargine, EU Lantus. Both in terms of PK and PD, similarity was demonstrated. Hence, from a PK/PD perspective Ondibta can be used as a biosimilar to Lantus.

2.5.5. Clinical efficacy

Efficacy is based on two phase 3 studies, where Ondibta is compared with Lantus in type 1 diabetes patients and in type 2 diabetes patients, respectively (Study GL-GLAT1-3001 and Study GL-GLAT2-3002, in the following named Study 3001 and Study 3002).

As stated in the guideline and in the CHMP advice, phase 3 studies are not deemed necessary if the quality criteria and PK/PD criteria are fulfilled, and therefore the phase 3 studies are considered supportive only.

Study	# Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goals	Design Control Type	Treatments (Dose, Route, Regimen)	Study Objective (s)	# Subjects by Arm Entered/ Completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Key (Secondary) Efficacy Endpoint and Results
GL-GLAT1-3001	Multicenter	A total of 718 subjects with T1DM were screened for enrollment. Of the 718 subjects screened, a total of 576 subjects (80.2%) were randomly assigned to treatment, The first subject was enrolled in this study on 31 Oct 2017.	Phase 3, multicenter, open-label, equivalence study Active comparator	GL Glargine Injection: SC, QD, dose determined by the physician EU Lantus: SC, QD, dose determined by the physician	Immunogenicity Safety Efficacy	Of the 576 subjects, 513 subjects (89.1%) completed the study	26 weeks	M=62.7 % (n=361) F=37.3 % (n=215)	Adults with a confirmed diagnosis of T1DM	Change from baseline in HbA1c at visit Week 26: • GL Glargine Injection: the mean (SD) change from baseline was -0.08 (0.756) • Lantus: the mean (SD) change from baseline was -0.03 (0.830)
GL-GLAT2-3002	Multicenter	A total of 802 subjects with T2DM were screened for enrolment. Of the 802 subjects screened, a total of 567 subjects (70.7%) were randomly assigned to treatment. The first subject was enrolled in this study on 31 Oct 2017	Phase 3, multicenter, open-label, equivalence study Active comparator	GL Glargine Injection: SC, QD, dose determined by the physician EU Lantus: SC, QD, dose determined by the physician	Immunogenicity Safety Efficacy	Of the 567 subjects, 515 subjects (90.8%) completed the study	26 weeks	M=60.1 % (n=341) F=39.9 % (n=226)	Adults with a confirmed diagnosis of T2DM	Change from baseline in HbA1c at visit Week 26: • GL Glargine Injection: the mean (SD) change from baseline in HbA1c was -0.41 (1.103) • Lantus: the mean (SD) change from baseline in HbA1c was -0.46 (1.118)

AIA=anti-insulin antibody; GL=Gan & Lee; HbA1c= glycated hemoglobin; QD=once daily; SC=subcutaneous; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus, SD=Standard deviation, EU=European Union; N=number of subjects

2.5.5.1. Dose response study(ies)

No dose response studies have been conducted for this proposed biosimilar insulin. This is acceptable. In the phase 3 studies, the patients' usual insulin dose is used in patients already treated with insulin, and in insulin naïve patients individual dosing is used according to the treating physician.

2.5.5.2. Main studies

Efficacy is based on two phase 3 studies, where Ondibta is compared with Lantus in an open label 26 weeks study in type 1 diabetes patients and in type 2 diabetes patients, respectively (Study 3001 and Study 3002).

As the two studies are similar in design, the studies will be reported jointly below for methods and results.

Study 3001 and 3002

Methods

Study Participants

Main inclusion criteria:

Both studies:

Male or nonpregnant, nonlactating female subjects between the ages of 18 and 75 years, inclusive

Study 3001:

- Subjects with a confirmed diagnosis of T1DM who had been on an approved basal and bolus insulin regimen for at least 6 months (the type or brand of insulin should not have changed in the 6 months before screening)
- Glycosylated haemoglobin (HbA_{1c}) ≤11.0%
- Body mass index (BMI) ≥19 kg/m2 and ≤35 kg/m2

Study 3002:

- Subjects with a confirmed diagnosis of T2DM who met 1 of the following:
  a) If insulin-naïve, subjects should have been on at least 2 approved OAMs for at least 12 weeks before screening, and the clinician has decided to add insulin therapy
  b) If already being treated with a basal insulin, subjects should have been treated with insulin for at least 6 months in addition to at least 1 approved OAM and must not have changed the type or brand of insulin within 6 months prior to screening
- Glycosylated hemoglobin (HbA_{1c}) values as follows:
  a) If insulin-naïve, HbA_{1c} ≤11.0%
  b) If previously on a basal insulin regimen, HbA_{1c} ≥7.0% and ≤11.0%
- Body mass index (BMI) ≤45 kg/m2

Main exclusion criteria

Both studies

- Previous use of a biosimilar insulin, either basal or bolus
- Documented AIA in the past
- Brittle T1DM or T2DM within the year before screening (e.g., multiple hospitalisations related to diabetes mellitus and/or severe hypoglycemia for which the subject required 3rd party assistance)
- Any severe, delayed sequela of diabetes mellitus (e.g., worsening end-stage renal disease, advanced coronary artery disease, or myocardial infarction within the year before screening) or autonomic peristaltic problems (e.g., gastroparesis).

Treatments

The study medication was Ondibta and EU Lantus, which were used in each study arm, respectively. The dose was determined by the treating physician and optimised prior to randomisation according to a dosing scheme based on fasting plasma glucose.

The use of CGM three times during the treatment period is acknowledged, although it was only used for monitoring and not for treatment adjustment.

Objectives

The primary objective of the phase 3 studies is assessment of immunogenicity.

Efficacy is considered a secondary objective. Non-inferiority between Ondibta and EU Lantus should be demonstrated.

Outcomes/endpoints

Key Secondary Endpoint:

- Change from baseline in HbA_{1c} at 26 weeks

Other efficacy endpoints:

- number and percentage of subjects who achieve an FBG test result of ≤ 6.0 mmol/L (≤ 108.0 mg/dL) at visit Week 26 for study 3001 and FBG ≤8.0 mmol/L (≤144.0 mg/dL) for study 3002
- The number and percentage of subjects who achieve a HbA_{1c} of < 7.0% at visit Week 26

Sample size

For both studies, 550 eligible participants were planned to be randomised in a 1:1 ratio across two study arms.

Randomisation and blinding (masking)

In Study 3001, participants are randomised in a 1:1 ratio to either Ondibta or Lantus treatment. Randomisation utilises a block design with varying block sizes and is stratified by country. Notably, when sites enrol fewer than 8 subjects, they are pooled within their respective countries. Considering that 57.8% of the sites (48 out of 83) fall into this category, the majority of the sites were pooled for analysis.

In Study 3002, participants are also randomised 1:1 to Ondibta or Lantus treatment. However, unlike Study 3001, there is no country stratification in Study 3002. All study sites are pooled for efficacy analyses in this study.

Blinding is not applicable in both studies as they are designed as open-label trials. However, to minimise bias, specific roles within the Sponsor and study team were blinded. This is endorsed.

Statistical methods

In both studies, the Full Analysis Set (FAS) comprised all randomised subjects, grouped by their planned treatment. Efficacy endpoints were analysed using the FAS based on each subject's randomised treatment. Of note, all participants who were randomised received at least one IP. Additionally, a Per Protocol Analysis Set (PP) was employed, including all randomised subjects who received at least one partial dose (Ondibta or EU Lantus) and had no significant protocol deviations during the initial 26 weeks of the study. The PP set was used for sensitivity analyses of confirmed positive anti-insulin antibodies (AIAs) and HbA_{1c}.

To ensure the robustness of results, multiple analysis sets were applied in both studies, involving different imputation strategies. Non-inferiority tests were conducted in both the FAS and PP analysis sets.

The testing of non-inferiority for the key secondary endpoint, Change from Baseline in HbA_{1c} at 26 weeks in both studies, was conducted using a margin of 0.4%. Since this test yielded a significant result, non-inferiority was then assessed using a margin of 0.3%. The 95% CI was estimated using a pattern mixture model that incorporated multiple imputations, which were analysed using ANCOVA. The model included treatment and the stratification factor of country as fixed effects, with baseline HbA_{1c} adjustment applied as a covariate.

For the secondary endpoint, the estimation of the difference in proportions of FBG test and HbA_{1c}, along with the corresponding 90% CI in the FAS, was carried out using a logistic regression model.

Multiple sensitivity analyses were performed using various analysis sets, imputation strategies, and the treatment policy estimand to support the main HbA_{1c} analysis.

Results

Participant flow

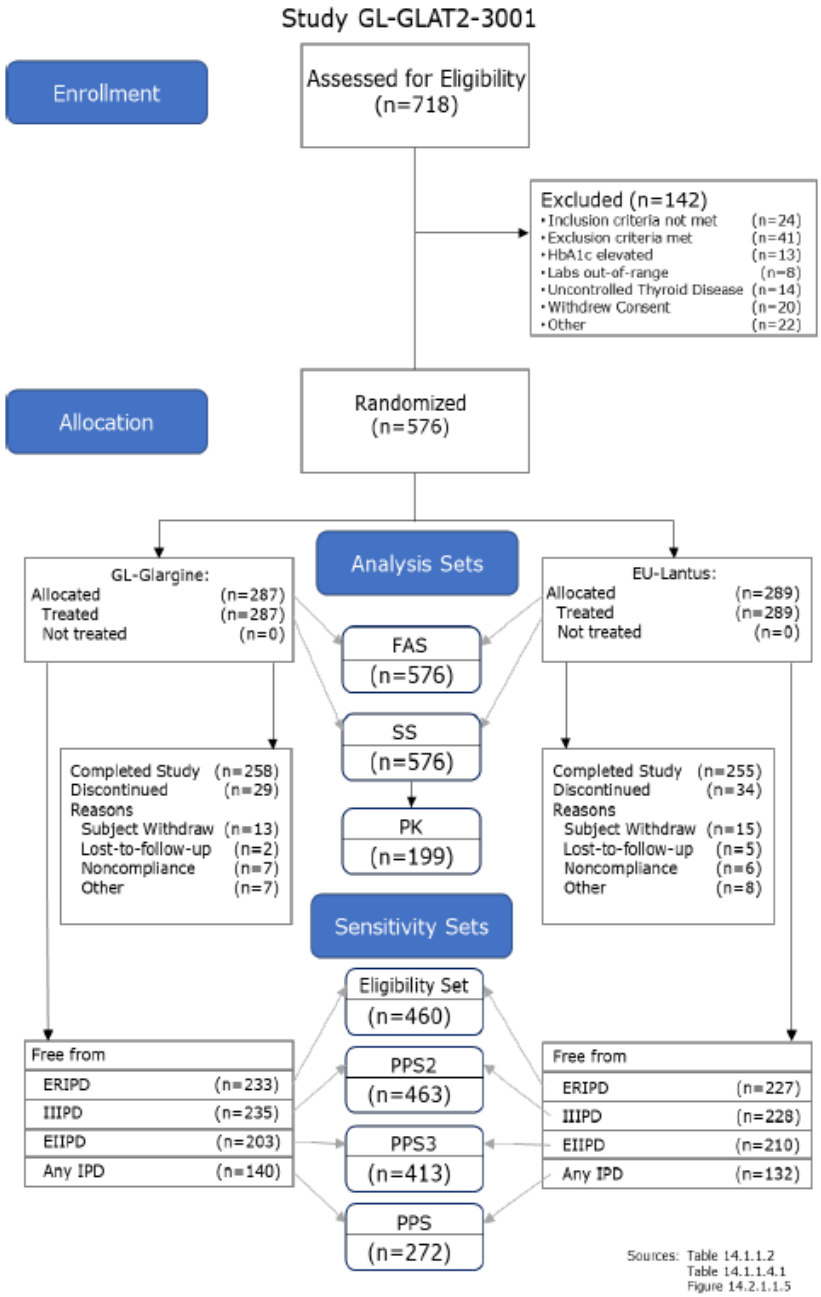
An overview of subject disposition and analysis sets in study 3001 and 3002 is presented in Figure 1 and 2, respectively.

In study 3001, 718 subjects were assessed for eligibility. Of those, 576 subjects with type 1 diabetes were randomised 1:1 to Ondibta (n=287) or Lantus (n=289). A total of 258 subjects in the Ondibta arm (89.9%) and 255 subjects in the Lantus arm (88.2%) completed the study.

In study 3002, 802 subjects were assessed for eligibility. Of those, 567 subjects with type 2 diabetes were randomised 1:1 to Ondibta (n=284) or Lantus (n=283). A total of 259 subjects in the Ondibta arm (91.2%) and 256 subjects in the Lantus arm (90.5%) completed the study.

The main reason for discontinuation in both studies and in both treatment arms was withdrawal by study subjects.

Study 3001:

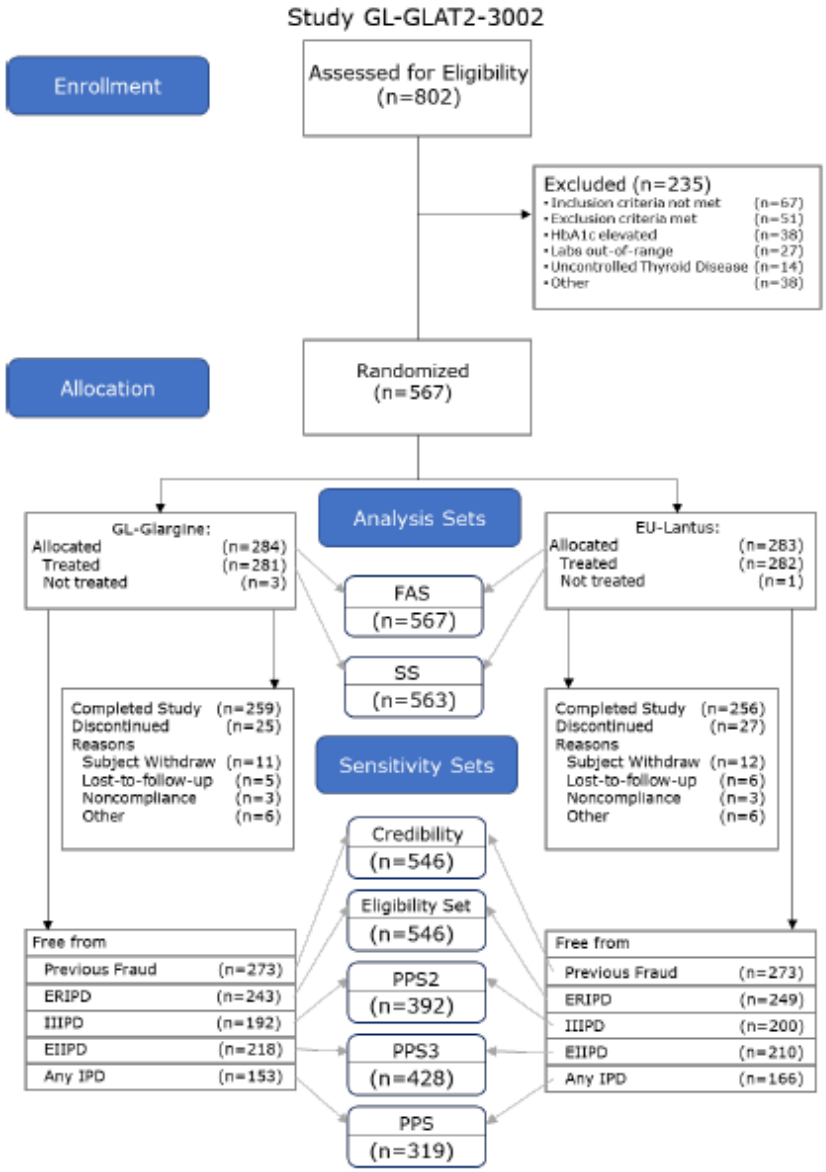


EIIPD=efficacy-interfering important protocol deviation; ERIPD=eligibility-related important protocol deviation; EU Lantus=European Union-approved Lantus; FAS=Full Analysis Set; GL Glargine (Injection)=Gan & Lee Insulin Glargine Injection; HbA1c=glycosylated hemoglobin; IPD=important protocol deviation; IIIPD=immunogenicity-interfering important protocol deviation; n=number of subjects; PK=pharmacokinetic(s); PPS=Per Protocol Analysis Set; PPS2/PPS3=Second/Third Per Protocol Analysis Set; SS=Safety Analysis Set.

Source: Table 14.1.1.1, Table 14.1.1.2, Table 14.1.1.4.1, and Figure 14.2.1.1.5

Figure 1: Disposition and analysis sets study 3001

Study 3002:



EIIPD=efficacy-interfering important protocol deviation; ERIPD=eligibility-related important protocol deviation; EU Lantus=European Union-approved Lantus; FAS=Full Analysis Set; GL Glargine (Injection)=Gan & Lee Insulin Glargine Injection; HbA1c=glycosylated hemoglobin; IPD=important protocol deviation; IIIPD=immunogenicity-interfering important protocol deviation; n=number of subjects; PK=pharmacokinetic(s); PPS=Per Protocol Analysis Set; PPS2/PPS3=Second/Third Per Protocol Analysis Set; SS=Safety Analysis Set.

Source: Table 14.1.1.1, Table 14.1.1.2, Table 14.1.1.4.1, and Figure 14.2.1.1.5

Figure 2: Disposition and analysis sets study 3002

Recruitment

For study 3001, first patient first visit was on 20th October 2017 and last patient last visit was on 19th August 2019.

For study 3002, first patient first visit was on 31st October 2017 and last patient last visit was on 21st August 2019.

Conduct of the study

In both studies, after recruitment was initiated a major protocol amendment was applied. This included, among others, change of HbA_{1c} at week 26 as primary endpoint to secondary endpoint. This is considered acceptable for this supportive study, where immunogenicity is considered the most important parameter.

Baseline data

Study 3001

Baseline demographics

In study 3001 in type 1 diabetes patients, the demographics were overall balanced between treatment groups besides for hypothyroidism that was more frequent in the Lantus arm (18.0% vs. 11.1%).

More men than women were included and the majority was white. Mean age was 46 years with a range from 18 years to 76 years. 65 subjects (11%) were between 65-75 years, and 3 subjects (two in the GL arm) were above 75 years. Mean body weight was 81 kg with a range from 45.6 kg to 136.0 kg.

The duration of diabetes was 21 years with a range from 1 to 61 years and mean HbA_{1c} was 8.1 with a range from 5.4 to 11.3. Specifically, there was no major difference between the two groups in HbA_{1c}. Mean HbA_{1c} was 8.11% in the Ondibta arm and 8.08% in the Lantus arm.

In the Lantus arm a marginally higher proportion of the patients had positive neutralising antibodies (3.1%) compared with the Ondibta arm (2.1%) at baseline.

Demographics and baseline characteristics (full analysis set) of study 3001

Characteristic	GL Glargine Injection (N=287)	EU Lantus (N=289)	Total (N=576)
Sex [n (%)]			
Female	103 (35.9)	112 (38.8)	215 (37.3)
Male	184 (64.1)	177 (61.2)	361 (62.7)
Race [n (%)]			
White	262 (91.3)	265 (91.7)	527 (91.5)

Black or African American	13 (4.5)	14 (4.8)	27 (4.7)
Asian	6 (2.1)	7 (2.4)	13 (2.3)
American Indian or Alaska Native	0	1 (0.3)	1 (0.2)
Native Hawaiian or other Pacific Islander	2 (0.7)	0	2 (0.3)
Other	2 (0.7)	1 (0.3)	3 (0.5)
Multiple	2 (0.7)	1 (0.3)	3 (0.5)
Ethnicity [n (%)]			
Hispanic or Latino	23 (8.0)	16 (5.5)	39 (6.8)
Not Hispanic or Latino	259 (90.2)	272 (94.1)	531 (92.2)
Not reported	4 (1.4)	1 (0.3)	5 (0.9)
Unknown	1 (0.3)	0	1 (0.2)
Age (years)			
n	287	289	576
Mean (SD)	45.7 (13.96)	46.7 (14.46)	46.2 (14.21)
Median	46	46	46
Q1, Q3	35, 57	36, 58	35, 58
Min, max	18, 76	18, 75	18, 76
Age group [n (%)]			
<65 years	256 (89.2)	252 (87.2)	508 (88.2)
≥65 years	31 (10.8)	37 (12.8)	68 (11.8)
Weight (kg)			
n	287	289	576
Mean (SD)	80.901 (13.4277)	81.548 (16.3993)	81.226 (14.9829)
Median	80.80	80.90	80.81
Q1, Q3	72.40, 88.60	69.09, 91.40	70.76, 90.53
Min, max	45.60, 122.70	48.80, 136.00	45.60, 136.00
BMI (kg/m^2)			
n	287	289	576
Mean (SD)	27.01 (3.875)	27.11 (4.237)	27.06 (4.058)
Country			
Czech Republic	24 (8.4)	25 (8.7)	49 (8.5)
Germany	29 (10.1)	28 (9.7)	57 (9.9)
Hungary	20 (7.0)	21 (7.3)	41 (7.1)
Poland	37 (12.9)	37 (12.8)	74 (12.8)
Spain	26 (9.1)	28 (9.7)	54 (9.4)
United States of America	151 (52.6)	150 (51.9)	301 (52.3)

Duration of diabetes (years)			
n	287	289	576
Mean (SD)	20.2 (13.88)	21.7 (13.95)	21.0 (13.92)
Median	18	20	19
Q1, Q3	8, 29	11, 30	10, 30
Min, max	1, 61	1, 60	1, 61
HbA1c (%)			
n	286	289	575
Mean (SD)	8.11 (1.229)	8.08 (1.267)	8.10 (1.247)
Median	8.0	8.0	8.0
Q1, Q3	7.2, 9.0	7.2, 8.9	7.2, 8.9
Min, max	5.4, 11.3	4.9, 11.0	4.9, 11.3
AIA result [n (%)]			
Negative	236 (82.2)	239 (82.7)	475 (82.5)
Positive	49 (17.1)	48 (16.6)	97 (16.8)
Nonreportable[a]	0	2 (0.7)	2 (0.3)
Missing	2 (0.7)	0	2 (0.3)
NAb result [n (%)]			
Negative[b]	44 (15.3)	38 (13.1)	82 (14.2)
Positive	6 (2.1)	9 (3.1)	15 (2.6)
Missing	1 (0.3)	1 (0.3)	2 (0.3)
Not tested[b]	236 (82.2)	241 (83.4)	477 (82.8)
Thyroid disease[c] [n (%)]			
Absence	243 (84.7)	210 (72.7)	453 (78.6)
Presence	44 (15.3)	79 (27.3)	123 (21.4)
Hypothyroidism	32 (11.1)	52 (18.0)	84 (14.6)
Hyperthyroidism	1 (0.3)	5 (1.7)	6 (1.0)
Structural abnormality	5 (1.7)	4 (1.4)	9 (1.6)

Thyroid cancer	0	0	0
Other	6 (2.1)	18 (6.2)	24 (4.2)

AIA=anti-insulin antibody; BMI=body mass index; CRF=case report form; EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; HbA1c=glycosylated hemoglobin; NAb=neutralizing antibody; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group; Q=quartile; SD=standard deviation.

Note: Thyroid disease is based on the Medical History – Thyroid Disease CRF page.

[a] The primary and backup samples were defrosted or had temperature excursion for these subjects.

[b] NAb was tested only if the AIA result was positive. The "Not tested" row contains subjects whose AIA result was negative and subjects with non-reportable or missing AIA results. Two subjects had negative NAb test results even though they had negative AIA results and are included in the "Negative" row.

[c] The Investigator could only report 1 thyroid disease record on the Medical History – Thyroid Disease CRF page, which is represented here. There were 2 subjects who had additional thyroid disease reported on the Medical History – General CRF page. One subject was reported with a "subclinical hypothyroidism" on the Thyroid CRF page and a hypothyroidism on the General CRF page. Another subject was reported with a "structural abnormality" on the Thyroid CRF page and a hypothyroidism on the General CRF page. One subject was included under "Other" as they had a thyroidectomy reported on the Thyroid CRF page as a result of thyroid cancer. The cancer was reported on the Medical History CRF page.

Source: Table 14.1.2.1

Medical history

The medical history was well balanced between treatment groups. 19.4% was diagnosed with hyperlipidaemia, 45.2% had vascular disorders where the main contribution was hypertension. 4.3% had a history of coronary artery disease, 3.1% had diabetic nephropathy and 2.3 had chronic kidney disease. Hence the study population was relatively healthy, which is a result of the exclusion criteria.

Antidiabetic treatment

Overall, insulin use prior to inclusion was balanced between treatment groups, although fewer subjects were treated with long-acting insulin in the Lantus group than the GL Insulin Glargine group (93.8% vs. 97.2%).

Prior Insulins and Analogues by ATC Classification and WHO Drug Dictionary Preferred Term (Full Analysis Set) study 3001

ATC Classification Level 4 Preferred Term	GL Glargine (N=287) [n (%)]	Lantus (N=289) [n (%)]	Total (N=576) [n (%)]
Any Prior Insulins and Analogues Medications	287 (100)	289 (100)	576 (100)
Insulins and Analogues For Injection, Long-Acting	279 (97.2)	271 (93.8)	550 (95.5)
Insulin Glargine	200 (69.7)	208 (72.0)	408 (70.8)
Insulin Detemir	46 (16.0)	32 (11.1)	78 (13.5)
Insulin Degludec	35 (12.2)	32 (11.1)	67 (11.6)
Insulin Human	1 (0.3)	0	1 (0.2)
Insulins and Analogues For Injection, Fast-Acting	16 (5.6)	13 (4.5)	29 (5.0)
Insulin Aspart	9 (3.1)	5 (1.7)	14 (2.4)
Insulin Lispro	5 (1.7)	4 (1.4)	9 (1.6)
Insulin Glulisine	0	4 (1.4)	4 (0.7)
Insulin Human	2 (0.7)	0	2 (0.3)
Insulins and Analogues For Injection, Intermediate-Acting	7 (2.4)	17 (5.9)	24 (4.2)
Insulin Human Injection, Isophane	7 (2.4)	17 (5.9)	24 (4.2)
Insulins and Analogues For Injection, Intermediate- Or Long-Acting Combined With Fast-Acting	1 (0.3)	0	1 (0.2)
Insulin Aspart; Insulin Aspart Protamine	1 (0.3)	0	1 (0.2)

ATC = Anatomical Therapeutic Chemical.
Note: Prior insulins and analogues are medications with an ATC code level 3 of 'A10A' with a start date prior to the date of randomization and an end date on or before the date of randomization and are coded using WHO Drug Dictionary version 2017 SEP DDE+HD B3.

Study 3002

Demographics

In study 3002 in type 2 diabetes patients, the demographics were overall balanced between treatment groups.

More men than women were included and the proportion of men was higher in the Ondibta arm than the Lantus arm (63.4% vs 56.9%). Mean age was 60.8 years with a range from 31 years to 76 years. 215 subjects (38%) were between 65-75 years, and 10 subjects (5 in each group) were above 75 years. Mean body weight was 98.1 kg with a range from 50.0 kg to 164.7 kg.

The duration of diabetes was 15.3 years with a range from 1 to 52 years and mean HbA_{1c} was 8.1 with a range from 5.4 to 11.3. Specifically, there was no major difference between the two groups in HbA_{1c}. Mean HbA_{1c} was 8.51% in the Ondibta arm and 8.49% in the Lantus arm.

No neutralising antibodies were observed in the type 2 diabetes population.

Demographics and baseline characteristics (full analysis set) of Study 3002

Characteristic	GL Glargine Injection (N=284)	EU Lantus (N=283)	Total (N=567)
Sex [n (%)]			
Female	104 (36.6)	122 (43.1)	226 (39.9)
Male	180 (63.4)	161 (56.9)	341 (60.1)
Race [n (%)]			
White	227 (79.9)	225 (79.5)	452 (79.7)
Black or African American	35 (12.3)	36 (12.7)	71 (12.5)
Asian	15 (5.3)	12 (4.2)	27 (4.8)
American Indian or Alaska Native	2 (0.7)	1 (0.4)	3 (0.5)
Native Hawaiian or other Pacific Islander	2 (0.7)	1 (0.4)	3 (0.5)

Other	1 (0.4)	5 (1.8)	6 (1.1)
Multiple	2 (0.7)	3 (1.1)	5 (0.9)
Ethnicity [n (%)]			
Hispanic or Latino	59 (20.8)	69 (24.4)	128 (22.6)
Not Hispanic or Latino	223 (78.5)	213 (75.3)	436 (76.9)
Not reported	2 (0.7)	1 (0.4)	3 (0.5)
Age (years)			
n	284	283	567
Mean (SD)	61.3 (8.98)	60.3 (8.95)	60.8 (8.97)
Median	63	61	62
Q1, Q3	56, 68	55, 67	56, 68
Min, max	31, 76	34, 75	31, 76
Age group [n (%)]			
<65 years	163 (57.4)	178 (62.9)	341 (60.1)
≥65 years	121 (42.6)	105 (37.1)	226 (39.9)
Weight (kg)			
n	284	283	567
Mean (SD)	98.011 (20.0532)	98.141 (20.5269)	98.076 (20.2732)
Median	97.09	96.80	97.00
Q1, Q3	84.90, 109.98	83.30, 113.18	83.80, 112.00
Min, max	52.73, 164.70	50.00, 160.40	50.00, 164.70
BMI (kg/m^2)			
n	284	283	567
Mean (SD)	33.49 (5.589)	33.59 (6.025)	33.54 (5.806)
Duration of diabetes (years)			
n	284	283	567
Mean (SD)	15.2 (7.96)	15.3 (7.92)	15.3 (7.93)
Median	15	14	15
Q1, Q3	10, 20	10, 20	10, 20
Min, max	1, 52	2, 48	1, 52
HbA1c (%)			
n	284	283	567
Mean (SD)	8.49 (1.027)	8.51 (1.029)	8.50 (1.027)
Median	8.3	8.3	8.3
Q1, Q3	7.7, 9.2	7.7, 9.2	7.7, 9.2

Characteristic	GL Glargine Injection (N=284)	EU Lantus (N=283)	Total (N=567)
Min, max	6.4, 11.0	6.4, 11.0	6.4, 11.0
AIA result [n (%)]			
Negative	252 (88.7)	263 (92.9)	515 (90.8)
Positive	5 (1.8)	1 (0.4)	6 (1.1)
Nonreportable[a]	27 (9.5)	19 (6.7)	46 (8.1)
NAb result [n (%)]			
Negative	5 (1.8)	1 (0.4)	6 (1.1)
Positive	0	0	0
Not tested[b]	279 (98.2)	282 (99.6)	561 (98.9)
Thyroid disease [n (%)]			
Absence	243 (85.6)	229 (80.9)	472 (83.2)
Presence	41 (14.4)	54 (19.1)	95 (16.8)
Hypothyroidism	34 (12.0)	45 (15.9)	79 (13.9)
Hyperthyroidism	2 (0.7)	0	2 (0.4)
Structural abnormality	1 (0.4)	1 (0.4)	2 (0.4)
Thyroid cancer	0	0	0
Other	4 (1.4)	8 (2.8)	12 (2.1)

AIA=anti-insulin antibody; BMI=body mass index; CRF=case report form; EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; HbA1c=glycosylated hemoglobin; max=maximum; min=minimum; Q1=first quartile; Q3=third quartile; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group; NAb=neutralizing antibody; SD=standard deviation.

Note: Thyroid disease is based on the Medical History – Thyroid Disease CRF page.

[a] The primary and backup samples were defrosted or had temperature excursion for these subjects.

[b] Neutralizing antibody was tested only if the AIA result was positive. This category contains those subjects whose AIA result was negative or whose sample was defrosted or had temperature excursion.

Source: Table 14.1.2.1

Medical history

The medical history was well balanced between treatment groups. 43.2% was diagnosed with hyperlipidaemia, 82.7% had vascular disorders where the main contribution was hypertension, 10.6% had a history of coronary artery disease, 4.1% had a history of myocardial infarction, 6.2% had chronic kidney disease, 21.9% had diabetic neuropathy and 14.3% peripheral neuropathy.

Hence the study population was representative of a type 2 diabetes population with multimorbidity.

Antidiabetic treatment

The use of insulin was well balanced between treatment groups at inclusion. 67.4% used long-acting insulin whereas 2.5% used fast acting insulin. This is representative of a type 2 diabetes population with relatively long duration of diabetes, which is also the case for the included population (mean duration of 15.6 years). During the study, more subjects in the Ondibta group used fast acting insulin (30.3% vs. 26.5%) and more subjects in the Lantus group used metformin (87.6% vs 84.2%).

Prior insulins and analogues by ATC classification and WHO drug dictionary preferred term (full analysis set) study 3002

ATC Classification Level 4 Preferred Term	GL Glargine (N=284) [n (%)]	Lantus (N=283) [n (%)]	Total (N=567) [n (%)]
Any Prior Insulins and Analogues Medications	204 (71.8)	203 (71.7)	407 (71.8)
Insulins and Analogues For Injection, Long-Acting	191 (67.3)	191 (67.5)	382 (67.4)
Insulin Glargine	137 (48.2)	132 (46.6)	269 (47.4)
Insulin Detemir	39 (13.7)	41 (14.5)	80 (14.1)
Insulin Degludec	16 (5.6)	23 (8.1)	39 (6.9)
Insulin Glargine; Lixisenatide	0	1 (0.4)	1 (0.2)
Insulins and Analogues For Injection, Intermediate-Acting	9 (3.2)	8 (2.8)	17 (3.0)
Insulin Human Injection, Isophane	9 (3.2)	8 (2.8)	17 (3.0)
Insulins and Analogues For Injection, Fast-Acting	7 (2.5)	7 (2.5)	14 (2.5)
Insulin Lispro	5 (1.8)	4 (1.4)	9 (1.6)
Insulin Aspart	2 (0.7)	3 (1.1)	5 (0.9)
Insulin Human	0	1 (0.4)	1 (0.2)
Insulins and Analogues For Injection, Intermediate- Or Long-Acting Combined With Fast-Acting	4 (1.4)	4 (1.4)	8 (1.4)
Insulin Human; Insulin Human Injection, Isophane	4 (1.4)	2 (0.7)	6 (1.1)
Insulin Lispro; Insulin Lispro Protamine Suspension	0	2 (0.7)	2 (0.4)

ATC = Anatomical Therapeutic Chemical.
Note: Prior insulins and analogues are medications with an ATC code level 3 of 'A10A' with a start date prior to the date of randomization and an end date on or before the date of randomization and are coded using WHO Drug Dictionary version 2017 SEP DDE+HD B3.

Numbers analysed

The main analysis was based on the full analysis set, and the sensitivity analysis on the per protocol analysis set.

In study 3001, 576 subjects were randomised and comprised the full analysis dataset. The per protocol analysis set (PPS) comprised of 272 subjects, PPS2 of 463 subjects and PP3 of 413 subjects.

In study 3002, 567 subjects were randomised and comprised the full analysis dataset. The per protocol analysis set (PPS) comprised of 319 subjects, PPS2 of 392 subjects and PP3 of 428 subjects.

Outcomes and estimation

Both studies met the HbA_{1c} non-inferiority margin of 0.3% (the EMA requirements): in patients with type 1 diabetes the HbA_{1c} difference between Ondibta and Lantus was -0.08 (95% CI: -0.26;0.09) and in patients with type 2 diabetes the HbA_{1c} difference was 0.06 (95% CI: -0.16;0.27).

The results were supported by the proportion of subjects reaching an FBG ≤6.0 mmol/l and HbA_{1c} < 7% in study 3001, although some information should be clarified, and the proportion of subjects reaching an FBG ≤ 8.0 mmol/l and HbA_{1c} < 7% in study 3002. Results are shown in the tables below.

Study 3001

Table 23 Analysis of Change From Baseline in HbA1c at Week 26 (Full Analysis Set)

Variable Statistic	GL Glargine Injection (N=287)	EU Lantus (N=289)	Difference in Change From Baseline[a,b]
Change from Baseline in HbA1c (%) at Week 26			
n[c]	286	289	
LS mean (SE)[a]	-0.08 (0.072)	0.00 (0.061)	-0.08 (0.089)
90% confidence interval[a]	(-0.20, 0.04)	(-0.10, 0.10)	(-0.23, 0.06)
95% confidence interval[a]	(-0.22, 0.06)	(-0.12, 0.12)	(-0.26, 0.09)

ANCOVA=analysis of covariance; EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; HbA1c=glycosylated hemoglobin; LS=least squares; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group; SE=standard error.

Notes: The Week 26 visit window is defined as Study Day 182 ± 28. One subject did not have baseline HbA1c data and is not included in the analysis.

[a] LS means, SEs, and confidence intervals for the change from baseline in HbA1c were estimated from an ANCOVA model that used multiple imputation. The model included 3 independent fixed factors: treatment, country, and a covariate for baseline HbA1c. Missing outcomes were imputed separately in each treatment group using outcomes in subjects who discontinued the study prior to Week 26 but returned to provide an HbA1c sample at Week 26.

[b] LS mean differences and associated confidence intervals are presented for the GL Glargine Injection group minus the EU Lantus treatment group.

[c] n is the number of subjects that contribute data at least once in the analysis model.

Source: Table 14.2.2.1.1

Table 27 Analysis of FBG Control at Week 26 (Full Analysis Set)

Measurements	GL Glargine Injection (N=287)	EU Lantus (N=289)	Treatment Difference (ASE)[a]	90% Confidence Interval
FBG control (FBG ≤6.0 mmol/L)				
No	248 (86.4)	247 (85.5)		
Yes	39 (13.6)	42 (14.5)	-0.9 (2.88)	(-5.6, 3.9)

ASE=asymptotic standard error; EU Lantus=European Union-approved Lantus; FBG=fasting blood glucose; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; N=number of subjects in a treatment group.

[a] Differences in proportions and associated confidence intervals are from a logistic regression model adjusted by country and are presented for the GL Glargine Injection group minus the EU Lantus treatment group.

Source: Table 14.2.2.2.2

Table 29 Analysis of HbA1c Control at Week 26 (Full Analysis Set)

Measurements	GL Glargine Injection (N=287)	EU Lantus (N=289)	Treatment Difference (ASE)[a]	90% Confidence Interval
HbA1c control (HbA1c <7.0%)				
No	241 (84.0)	245 (84.8)		
Yes	46 (16.0)	44 (15.2)	0.7 (2.99)	(-4.2, 5.6)

ASE=asymptotic standard error; EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; HbA1c =glycosylated hemoglobin; IP=Investigational Product; N=number of subjects in a treatment group.

Note: For HbA1c, all results are included regardless of scheduled/unscheduled status and regardless of whether the subject was still on IP or not.

[a] Differences in proportions and associated confidence intervals are from a logistic regression model adjusted by country and are presented for the GL Glargine Injection group minus the EU Lantus treatment group.

Source: Table 14.2.2.2.2

Study 3002

Table 21 Analysis of Change From Baseline in HbA1c at Week 26 (Full Analysis Set)

Variable Statistic	GL Glargine Injection (N=284)	EU Lantus (N=283)	Difference in Change From Baseline[a,b]
Change from baseline in HbA1c (%) at Week 26			
n[c]	284	283	
LS mean (SE)[a]	-0.39 (0.079)	-0.45 (0.079)	0.06 (0.111)
90% confidence interval[a]	(-0.52, -0.26)	(-0.58, -0.32)	(-0.13, 0.24)
95% confidence interval[a]	(-0.55, -0.24)	(-0.60, -0.29)	(-0.16, 0.27)

ANCOVA=analysis of covariance; EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; HbA1c=glycosylated hemoglobin; LS=least squares; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group; SE=standard error.

[a] LS means, SEs, and confidence intervals for the change from baseline in HbA1c were estimated from an ANCOVA model that used multiple imputation. The model included 2 independent fixed factors, treatment and a covariate for baseline HbA1c. Missing outcomes were imputed separately in each treatment group using outcomes in subjects who discontinued the study prior to Week 26 but returned to provide an HbA1c sample at Week 26.

[b] LS mean differences and associated confidence intervals are presented for the GL Glargine Injection group minus the EU Lantus treatment group.

[c] n is the number of subjects that contribute data at least once in the analysis model.

Source: Table 14.2.2.1.1

Table 25 Analysis of FBG Control at Week 26 (Full Analysis Set)

Measurements	GL Glargine Injection (N=284)	EU Lantus (N=283)	Treatment Difference (ASE)[a]	90% Confidence Interval
FBG control (FBG ≤8.0 mmol/L)				
No	151 (53.2)	145 (51.2)		
Yes	133 (46.8)	138 (48.8)	-1.9 (4.19)	(-8.8, 5.0)

ASE=asymptotic standard error; EU Lantus=European Union-approved Lantus; FBG=fasting blood glucose; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; N=number of subjects in a treatment group.

Note: All subjects in the Full Analysis Set are included in the FBG control analysis. Subjects with a Week 26 missing value for a glycemic control parameter are categorized as having failed to achieve glycemic control for that parameter.

[a] Differences in proportions and associated confidence intervals are from a logistic regression model and are presented for the GL Glargine Injection group minus the EU Lantus treatment group.

Source: Table 14.2.2.2.2

Table 27 Analysis of HbA1c Control at Week 26 (Full Analysis Set)

Measurements	GL Glargine Injection (N=284)	EU Lantus (N=283)	Treatment Difference (ASE)[a]	90% Confidence Interval
HbA1c control (HbA1c <7.0%)				
No	249 (87.7)	246 (86.9)		
Yes	35 (12.3)	37 (13.1)	-0.8 (2.80)	(-5.4, 3.9)

ASE=asymptotic standard error; EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; HbA1c =glycosylated hemoglobin; N=number of subjects in a treatment group.

Note: All subjects in the Full Analysis Set are included in the HbA1c control analysis. Subjects with a Week 26 missing value for a glycemic control parameter are categorized as having failed to achieve glycemic control for that parameter.

[a] Differences in proportions and associated confidence intervals are from a logistic regression model and are presented for the GL Glargine Injection group minus the EU Lantus treatment group.

Source: Table 14.2.2.2.2

Ancillary analyses

Sensitivity analysis

Sensitivity analysis of the per protocol populations and tipping point analyses supported the main analyses of HbA_{1c}.

Subgroup analysis

In study 3001 and 3002 there were no marked differences in HbA_{1c} between the two treatment arms in each subgroup, besides of non-whites in study 3001 and those who have a protocol deviation in study 3002. The numerical difference of 0.28% and 0.49%, respectively, is considered due to the low number of subjects in those groups.

Study 3001:

Table Subgroup Analysis: Change from Baseline in HbA_{1c} (%) at Week 26 (Full Analysis Set)

Subgroup Change from Baseline	GL Glargine (N=287) LS mean[a] (n)[b]	Lantus (N=289) LS mean[a] (n)[b]	Difference (90% CI)[c]
Primary Result HbA1c	-0.08 (286)	0.00 (289)	-0.08 (-0.23, 0.06)
Gender			
Male	-0.11 (184)	-0.03 (177)	-0.08 (-0.25, 0.09)
Female	-0.04 (102)	0.06 (112)	-0.09 (-0.32, 0.13)
Age			
< 65 years old	-0.09 (255)	0.00 (252)	-0.10 (-0.25, 0.06)
>= 65 years old	-0.01 (31)	0.02 (37)	-0.03 (-0.38, 0.33)
Race			
White	-0.09 (261)	0.02 (265)	-0.11 (-0.26, 0.04)
Non-White	0.30 (25)	0.02 (24)	0.28 (-0.21, 0.77)
BMI			
Obese (BMI >= 30)	-0.14 (66)	-0.03 (68)	-0.11 (-0.40, 0.18)
Non-Obese (BMI < 30)	-0.04 (220)	0.00 (221)	-0.04 (-0.20, 0.12)
Menopausal Status			
Pre-Menopause	-0.06 (56)	0.10 (55)	-0.16 (-0.46, 0.14)
Post-Menopause	-0.03 (46)	0.02 (57)	-0.04 (-0.37, 0.28)
ERIPD			
Without ERIPD	-0.08 (233)	0.00 (227)	-0.08 (-0.22, 0.06)
With ERIPD	-0.10 (53)	-0.01 (62)	-0.08 (-0.44, 0.28)

HbA1c = Glycated Haemoglobin; LS = Least Squares; CI = Confidence Interval; BMI = Body Mass Index; ERIPD = Eligibility Related Important Protocol Deviation.
Note: Week 26 visit window is defined as Study Day 182 ± 28. One subject is missing baseline HbBA1c and is not included in the analysis.
a. LS means, standard errors and confidence intervals for the change from baseline in HbA1c were estimated from an ANCOVA model that used multiple imputation. The model included three independent fixed factors, treatment, country, and a covariate for baseline HbA1c. Missing outcomes were imputed separately in each treatment group using outcomes in subjects who completed the study.
b. n is the number of subjects that contribute data at least once in the analysis model.
c. LS mean differences and associated confidence intervals are presented for GL Glargine arm minus the Lantus treatment arm

Study 3002

Table Subgroup analysis: Change from Baseline in HbA_{1c} (%) at Week 26 (Full Analysis Set)

Subgroup Change from Baseline	GL Glargine Injection (N=284) LS Mean[a](n)[b]	EU Lantus (N=283) LS Mean[a] (n)[b]	Difference (90% CI)[c]
Primary Result HbA1c	-0.39 (284)	-0.45 (283)	0.06 (-0.13, 0.24)
Gender			
Male	-0.31 (180)	-0.34 (161)	0.03 (-0.19, 0.24)
Female	-0.52 (104)	-0.59 (122)	0.08 (-0.21, 0.37)
Age			
< 65 years old	-0.44 (163)	-0.50 (178)	0.07 (-0.17, 0.30)
>= 65 years old	-0.32 (121)	-0.36 (105)	0.04 (-0.20, 0.29)
Race			
White	-0.36 (227)	-0.41 (225)	0.05 (-0.16, 0.26)
Non-White	-0.52 (57)	-0.58 (58)	0.07 (-0.26, 0.40)
BMI			
Obese (BMI >= 30)	-0.47 (207)	-0.48 (198)	0.01 (-0.20, 0.22)
Non-Obese (BMI < 30)	-0.18 (77)	-0.36 (85)	0.17 (-0.13, 0.47)
Menopausal Status			
Pre-Menopause	-0.88 (16)	-0.83 (13)	-0.05 (-0.81, 0.72)
Post-Menopause	-0.45 (88)	-0.56 (109)	0.11 (-0.18, 0.40)
ERIPD			
Without ERIPD	-0.43 (245)	-0.42 (250)	-0.01 (-0.19, 0.17)
With ERIPD	0.16 (39)	-0.65 (33)	0.49 (-0.05, 1.02)

ANCOVA=analysis of covariance; BMI=body mass index; CI=confidence interval; ERIPD=Eligibility-Related Important Protocol Deviation; EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; HbA1c=glycated haemoglobin; LS=least squares; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group.
a LS means, standard errors, and confidence intervals for the change from baseline in HbA1c were estimated from an ANCOVA model that used multiple imputation. The model included 2 independent fixed factors, treatment, and a covariate for baseline HbA1c. Missing outcomes were imputed separately in each treatment group using outcomes in subjects who completed the study.
b n is the number of subjects that contributed data at least once in the analysis model.
c LS mean differences and associated CIs are presented for the GL Glargine Injection group minus the EU Lantus treatment group.

2.5.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials			
Study 3001	65/576	3/576	0/576
Study 3002	215/567	10/567	0/567

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant has conducted 2 phase 3 studies in type 1 diabetes and type 2 diabetes patients, respectively (Study GL-GLAT1-3001 and Study GL-GLAT2-3002, in the following named Study 3001 and Study 3002). As stated in the guideline and in the CHMP Scientific Advice, phase 3 studies are not deemed necessary if the quality criteria and PK/PD criteria are fulfilled, and therefore the phase 3 studies are considered supportive only.

Both studies were open-label, randomised, multicentre studies where Ondibta was compared with Lantus in adults with type 1 or type 2 diabetes. Patients with type 2 diabetes were allowed to be insulin naïve or treated with insulin before entering the study. Type 1 or type 2 diabetes patients should have been on stable insulin treatment for at least 6 months before inclusion. Insulin-naïve type 2 diabetes patients should receive at least 2 oral antidiabetic medications to be included. Patients with severe, delayed sequala of diabetes e.g. worsening end stage renal disease, advanced coronary artery disease, or myocardial infarction within the year before screening or gastroparesis were excluded from the study. Hence the study populations with type 1 or type 2 diabetes do not reflect the overall adult type 1 and type 2 diabetes population. However, it was agreed that those patients were not included due to the severity of micro-and macrovascular complications, and it was agreed that the results can be extrapolated to patients with severe micro- and macrovascular complications.

It was considered acceptable that newly diagnosed patients with type 1 diabetes were also not included as those patients require very tight follow-up and titration of insulin after the diagnosis has been established. Nevertheless, the results of the study are considered acceptable to be extrapolated to newly diagnosed type 1 diabetes patients. Newly diagnosed type 2 diabetes patients are usually too early in the disease course to be treated with insulin, it is therefore not considered relevant to include them for an insulin trial.

The study medication in both studies was Ondibta and EU Lantus, which were used in each study arm, respectively. The dose was determined by the treating physician and optimised prior to randomisation according to a dosing scheme based on fasting plasma glucose. This is acknowledged and could prevent treatment bias due to the open label design. During the study, the dose was titrated by the physician based on the patients' needs.

Continuous glucose monitoring was used 3 times during the study. The use of personal CGM devices—either prior to enrolment or during the study—was allowed in all three studies. In study 1002, use of CGM was evenly distributed across treatment arms. In studies 3001 and 3002, the Applicant did not report on the distribution of CGM use in the treatment arms. However, it is noted that all treatment decisions were based on glucometer values, not on CGM data.

The main objective of the study was to assess immunogenicity. The key secondary efficacy endpoint was change in HbA_{1c} from baseline to week 26. The two supportive secondary efficacy endpoints were number and percentage of subjects with FBG ≤ 6.0 mmol/L (for type 1 diabetes) at week 26 and FBG ≤ 8.0 mmol/L (for type 2 diabetes) at week 26, and the number and percentage of subjects with HbA_{1c} of < 7.0% at week 26).

A total number of 500 subjects were to be included in each of the studies. Blinding was not applicable in both studies as they were designed as open-label trials due to the different devices. However, to minimise bias, specific roles within the Sponsor and study team were blinded. This is endorsed. The assessments of AIAs were also conducted in a blinded manner.

The testing of non-inferiority for the key secondary endpoint, Change from Baseline in HbA_{1c} at 26 weeks in both studies, was conducted using a margin of 0.4%. Since this test yielded a significant result, non-inferiority was then assessed using a margin of 0.3%. The 95% CI was estimated using a pattern mixture model that incorporated multiple imputations, which were analysed using ANCOVA. The model included treatment and the stratification factor of country as fixed effects, with baseline HbA_{1c} adjustment applied as a covariate.

The non-inferiority margin of 0.3 is preferred based on the EMA diabetes guideline (CPMP/EWP/1080/00), which has also been stated in the EMA scientific advice. As the data is analysed in a hierarchical manner, the Applicant's approach is considered acceptable.

For the secondary endpoint, the estimation of the difference in proportions of FBG test and HbA_{1c}, along with the corresponding 90% CI in the FAS, was carried out using a logistic regression. Since this analysis used a 90% CI, these endpoints are considered supplementary. The Applicant provided 95% CIs for the difference in proportions of FBG test and $HbA_{1c,}$ based on the same analysis previously reported with 90% CIs, yielding similar conclusion.

Multiple sensitivity analyses were performed using various analysis sets, imputation strategies, and the treatment policy estimand to support the main HbA_{1c} analysis.

The utilisation of statistical methods for measuring efficacy endpoints was accepted.

Efficacy data and additional analyses

In study 3001, 576 subjects with type 1 diabetes were randomised 1:1 to GL Insulin Glargine (n=287) or Lantus (n=289) group. A total of 258 subjects in the Ondibta arm (89.9%) and 255 subjects in the Lantus arm (88.2%) completed the study.

In study 3002, 567 subjects with type 2 diabetes were randomised 1:1 to Ondibta (n=284) or Lantus (n=283) group. A total of 259 subjects in the Ondibta arm (91.2%) and 256 subjects in the Lantus arm (90.5%) completed the study.

The baseline characteristics, medical history and antidiabetic treatment were well balanced between the treatment arms. Overall, the study population represented a mixed type 1 and type 2 diabetes populations, where long-acting insulin is prescribed to subjects with newly diagnosed type 1 diabetes and subjects with severe complications.

Both studies met the HbA_{1c} non-inferiority margin of 0.3% (the EMA requirements): in patients with type 1 diabetes the HbA_{1c} difference between GL Insulin Glargine and Lantus was -0.08 (95% CI: -0.26;0.09) and in patients with type 2 diabetes the HbA_{1c} difference was 0.06 (95% CI: -0.16;0.27).

The main HbA_{1c} results were supported by the proportion of subjects with HbA_{1c} <7% and FBG ≤6.0 mmol/l (type 1 diabetes) and FBG ≤8.0 mmol/l (type 2 diabetes). The sensitivity analyses supported the results from the main analyses in both studies.

The subgroup analyses showed similar results between gender, age, race, BMI, menopausal status and protocol deviations in both studies, with an exception of non-whites in study 3001 and those who have a protocol deviation in study 3002. There was a numerical difference of HbA_{1c} of 0.49% in study 3002 between those with and without protocol deviations. However, based on the baseline characteristics in subjects with and without ERPIDs, no significant impact of ERIPDs on the results is anticipated.

2.5.7. Conclusions on the clinical efficacy

The phase 3 studies are not considered the pivotal studies, but the results of the two studies in type 1 and type 2 diabetes patients demonstrated that Ondibta was non-inferior to Lantus after 26 weeks of treatment, which supports the biosimilarity between Ondibta and Lantus.

2.5.8. Clinical safety

The safety results in this submission are presented for the pivotal PK/PD similarity study and for the phase 3 studies. The CSR of Pilot study GL-GLA-001 is not included in this submission.

A summary of clinical safety studies included in this submission is presented in 2.7.4-2.

Table 2.7.4- 2: Description of Clinical Safety Studies

Study	# Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment / Enrollment Goals	Design Control Type	Treatments (Dose, Route, Regimen)	Study Objective(s)	# Subjects by Arm Entered / Completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Key Safety Endpoint(s) and Results
Pivotal Study										
GL-GLA-CT1002	2 centers in Germany	10 Jul 2018 Study complete (LSLV): 28 Nov 2018 114 enrolled of 114 planned subjects	Phase 1, randomized, double-blind, 3-way crossover, 3-treatment study Active comparator	GL glargine injection: 0.5 U/kg, SC, QD US Lantus: 0.5 U/kg, SC, QD EU Lantus: 0.5 U/kg, SC, QD	Biosimilarity (PK/PD) Safety	Randomized: 114 GL Glargine Injection: 110 (96.5%) US Lantus:111 (97.4%) EU Lantus:112 (98.2%)	4 weeks	114/0 43.0 (18-64) Median age range: 43.0 (18-64) years	Male adults with T1DM	TEAEs: GL Glargine Injection: 19.1% US Lantus: 26.1% EU Lantus: 21.4% Clinical laboratory parameters: An elevated Creatinine Kinase (CK) level prior to dosing and a mild and transient hypokalemia reported as AE, there were no clinically significant findings or changes in safety laboratory test results. There were no clinically significant findings or changes in vital signs, ECGs, and physical examination results.

Study	# Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment / Enrollment Goals	Design Control Type	Treatments (Dose, Route, Regimen)	Study Objective(s)	# Subjects by Arm Entered / Completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Key Safety Endpoint(s) and Results
Phase 3 Studies										
GL-GLAT1-3001	Multicenter Total Study Centers = 83 Czech Republic (7), Germany (6), Hungary (7), Poland (7), Spain (8), United States of America (48)	Study period: 31 Oct 2017 to 19 Aug 2019 A total of 718 subjects with T1DM were screened for enrollment. Of the 718 subjects screened, a total of 576 subjects (80.2%) were randomly assigned to treatment.	Phase 3, multicenter, open-label, equivalence study Active comparator	GL glargine injection: SC, QD, dose determined by the physician Lantus: 100 U/mL, SC, QD	Immunogenicity Safety Efficacy	Of the 576 subjects, 513 subjects GL Glargine injection (287) and EU Lantus (289) (89.1%) completed the study	26 weeks	M=62.7 % (n=361) F=37.3 % (n=215) Median age range: 46 (18 to 76) years	Adults with a confirmed diagnosis of T1DM	Percentage of subjects who develop treatment-induced AIA: GL Glargine Injection: 25.8% Lantus: 25.3% Percentage of subjects with negative AIA at baseline who develop confirmed positive AIA after baseline and up to visit Week 26: GL Glargine Injection: 26.7% Lantus: 24.7% Percentage of subjects with confirmed positive AIA at baseline and at least a 4-fold increase in titers after baseline and up to visit Week 26: GL Glargine Injection: 22.4% Lantus: 29.2% Mean change from baseline in AIA titers after baseline and up to visit

Study	# Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment / Enrollment Goals	Design Control Type	Treatments (Dose, Route, Regimen)	Study Objective(s)	# Subjects by Arm Entered / Completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Key Safety Endpoint(s) and Results
										Week 26: GL Glargine Injection: 4.8 (88.88) Lantus: -42.5 (332.90) Percentage of subjects with confirmed positive AIA after baseline and up to visit Week 26 who develop any anti-insulin neutralizing antibodies after baseline and up to visit Week 26: GL Glargine Injection: 24.1% Lantus: 26.7% Percentage of subjects with confirmed positive AIA after baseline and up to visit Week 26: GL Glargine Injection: 35.5% Lantus: 35.6% TEAEs: GL Glargine Injection: 90.2% Lantus: 92.4%

Study	# Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment / Enrollment Goals	Design Control Type	Treatments (Dose, Route, Regimen)	Study Objective(s)	# Subjects by Arm Entered / Completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Key Safety Endpoint(s) and Results
GL-GLAT2-3002	Multicenter	Study period: 31 Oct 2017 to 21 Apr 2019 A total of 802 subjects with T2DM were screened for enrollment. Of the 802 subjects screened, a total of 567 subjects (70.7%) were randomly assigned to treatment	Phase 3, multicenter, open-label, equivalence study Active comparator	GL glargine injection: SC, QD, dose determined by the physician Lantus: 100 U/mL, SC, QD	Immunogenicity Safety Efficacy	Of the 567 subjects, 515 (91.5%) subjects completed the study. GL Glargine injection 259 (92.2%) and EU Lantus 256 (90.8%) completed the study	26 weeks	M=60.1 % (n=341) F=39.9 % (n=226) Median age range: 62 (31 - 76) years	Adults with a confirmed diagnosis of T2DM	Percentage of subjects who develop treatment-induced AIA: GL Glargine Injection: 19.2% Lantus: 21.3% Percentage of subjects with negative AIA at baseline who develop confirmed positive AIA after baseline and up to visit Week 26: GL Glargine Injection: 16.9% Lantus: 20.2% Percentage of subjects with confirmed positive AIA at baseline and at least a 4-fold increase in titers after baseline and up to visit Week 26: GL Glargine Injection: 0 Lantus: 0 Mean change from baseline in AIA titers after baseline and up to visit Week 26: GL Glargine

Study	# Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment / Enrollment Goals	Design Control Type	Treatments (Dose, Route, Regimen)	Study Objective(s)	# Subjects by Arm Entered / Completed	Duration	Gender M / F Median Age (Range)	Diagnosis Inclusion Criteria	Key Safety Endpoint(s) and Results
										Injection: 23.5 (19.09) Lantus: -3.0 (NA) Percentage of subjects with confirmed positive AIA after baseline and up to visit Week 26 who develop any anti-insulin neutralizing antibodies after baseline and up to visit Week 26: GL Glargine Injection: 10.0% Lantus: 18.8% Percentage of subjects with confirmed positive AIA after baseline and up to visit Week 26: GL Glargine Injection: 20.6% Lantus: 21.6% TEAEs: GL Glargine Injection: 80.1% Lantus: 81.6%
AIA=anti-insulin antibody; ECG=electrocardiogram; GL=Gan & Lee; HbA1c=glycosylated hemoglobin; (I)U=(international) units; QD=once daily; SC=subcutaneous; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus										

2.5.8.1. Patient exposure

A total of 678 subjects have been exposed to Ondibta, with a median duration of exposure of 3.5 months (range: 0.03 -6.07 months). A total of 1252 subjects across studies have been exposed to Ondibta (Ondibta 100 U/mL) with US and EU Lantus.

Exposure to Ondibta across Studies GL-GLA-CT1002, GL-GLAT1-3001, and GL-GLAT2-3002 is summarised in Table 2.7.4-3.

Table 2.7.4-3: Extent of Exposure to GL Glargine Injection

Study/Phase	Dose/Duration of Treatment (weeks)	Age Range (Years)	No. of Patients
Pivotal Study/ (GL-GLA-CT1002)	A single s.c. dose of GL glargine injection at 0.5 U/kg body weight from 3 mL pre-filled pen. The duration of trial per subject was about 4 weeks (range: 3-12 weeks).	18 to 64 years	110
T1DM/ study (GL-GLAT1-3001)	Individual subject to received subcutaneously daily 100 U/mL of GL Glargine injection or EU Lantus treatment for 26 weeks.	18-76 years	287
T2DM/study (GL-GLAT2-3002)	Individual subject to received subcutaneously daily 100 U/mL of GL Glargine injection or EU Lantus treatment for 26 weeks.	31-76 years	281
TOTAL	Median*: 3.5 months (0.03 – 6.07 months)	18-76 years	678
PD=pharmacodynamics; PK=pharmacokinetics; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus			

Since the posology in study 1002 is only a single dose administration, the safety data presented below will focus on data from the phase 3 studies.

2.5.8.2. Adverse events

Study 1002

In this single dose study, 19% of the subjects in the Ondibta arm experienced a TEAE compared to 21% in the EU Lantus arm. The number of and the most frequent TEAEs (hypoglycaemia and headache) were similar.

Study GL-GLAT1-3001

TEAEs were assessed at screening, at each treatment visit, and at the end-of-treatment visit. SAEs were queried at follow-up (30±3 days after visit 9).

Of 287 subjects treated with Ondibta, 259 subjects (90.2%) and of 289 subjects treated with EU Lantus 267 subjects (92.4%) had at least 1 TEAE. The most frequently reported TEAEs (reported in ≥5% of subjects in any treatment group) were hypoglycaemia (85.7% of subjects in the Ondibta treatment group and 87.9% of subjects in the EU Lantus treatment group), nasopharyngitis (9.4% of subjects in the Ondibta treatment group and 8.3% of subjects in the EU Lantus treatment group), and upper respiratory tract infection (5.6% of subjects in the Ondibta treatment group and 2.4% of subjects in the EU Lantus treatment group). No TEAEs had a ≥5% difference in event rate between treatment groups. The proportions of subjects experiencing TEAEs overall and the most common TEAEs were similar between treatment groups. Overall, the incidence of TEAEs was consistent with treatment expectations, and no new safety signals were identified.

Adverse Events of Special Interest

Hypoglycemia was the only AE considered to be an AESI. Subjects brought their Hypoglycemic Events Record to each visit.

During the 26-week treatment period, similar percentages of subjects experienced any hypoglycemic TEAE in the Ondibta treatment group (85.7%) and the EU Lantus treatment group (87.9%) (Table 34). The total number of events was similar between treatment groups (7041 and 6866, respectively).

Table 34 Summary of Hypoglycemic TEAEs by Test Method (Safety Analysis Set)

Category Preferred Term	GL Glargine Injection (N=287) [n (%) m]	EU Lantus (N=289) [n (%) m]
Any hypoglycemic TEAE	246 (85.7) 7041	254 (87.9) 6866
Any hypoglycemic TEAE based on lowest blood glucose level by fingerstick or venous blood draw	228 (79.4) 6625	238 (82.4) 6375

Table 34 Summary of Hypoglycemic TEAEs by Test Method (Safety Analysis Set)

Category Preferred Term	GL Glargine Injection (N=287) [n (%) m]	EU Lantus (N=289) [n (%) m]
Any hypoglycemic TEAE based on lowest blood glucose level by other method	23 (8.0) 233	23 (8.0) 303

CGM=continuous glucose monitor; EU Lantus=European Union-approved Lantus; FGM=fasting glucose monitor; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; IP=investigational product; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group; TEAE=treatment-emergent adverse event.

Note: Adverse events were coded using MedDRA Version 22.0. For each category, a subject is included only once, even if they experienced multiple events in that category. A TEAE is an event that started or worsened in severity on or after the day of the first dose of IP but not more than 30 days after the subject's last dose of IP. Other methods include but were not limited to the following: Freestyle Libre, CGM, FGM, Dexcom, etc.

Source: Table 14.3.2.5

Study GL-GLAT2-3002

TEAEs were assessed at screening, at each treatment visit, and at the end-of-treatment visit. SAEs were queried at follow-up (30±3 days after visit 9).

Of 281 subjects treated with Ondibta 225 subjects (80.1%) reported 1716 TEAEs. Of 282 subjects treated with EU Lantus 230 subjects (81.6%) reported 1598 TEAES. Overall, the incidence of TEAEs was consistent with treatment expectations, and no new safety signals were identified. The proportion of subjects experiencing TEAEs overall and the most common TEAEs was similar between treatment groups. The most frequently reported AEs (reported in ≥5% of subjects in any treatment group) were **hypoglycaemia** (150 [53.4%] of subjects reported 1259 TEAEs in the Ondibta treatment group and 146 [51.8%] of subjects reported 1109 TEAEs in the EU Lantus treatment group), upper respiratory tract infection (23 [8.2%] of subjects reported 25 TEAEs in the Ondibta treatment group and 19 [6.7%] of subjects reported 19 TEAEs in the EU Lantus treatment group), hyperglycaemia (4.3% of subjects in the Ondibta treatment group and 5.7% of subjects in the EU Lantus treatment group), and diarrhea (3.9% of subjects in the Ondibta treatment group and 5.0% of subjects in the EU Lantus treatment group). Overall, there was no clinically meaningful difference noted between GL Insulin and reference product in occurrence of common adverse events across all studies conducted.

Adverse Events of Special Interest

In this study, hypoglycaemia was the only AE considered to be an AESI. Subjects brought their Hypoglycaemic Events Record to each visit.

During the 26-week treatment period, similar percentages of subjects experienced any hypoglycaemic TEAE in the Ondibta treatment group (53.4%) and in the EU Lantus treatment group (51.8%) (Table 32). The total number of events was similar between treatment groups (1259 and 1109, respectively). No subjects had hypoglycaemic SAEs.

Table 32 Summary of Hypoglycemic TEAEs by Preferred Term (Safety Analysis Set)

Category Preferred Term	GL Glargine Injection (N=281) [n (%) m]	EU Lantus (N=282) [n (%) m]
Any hypoglycemic TEAE	150 (53.4) 1259	146 (51.8) 1109
Hypoglycaemia	150 (53.4) 1259	146 (51.8) 1109

EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group; TEAE=treatment-emergent adverse event.

Note: Adverse events were coded using MedDRA Version 22.0. For each System Organ Class and Preferred Term, subjects are included only once, even if they experienced multiple events in that System Organ Class or Preferred Term. Treatment-emergent adverse event is an event that newly appears having been absent pretreatment or worsens relative to the pretreatment state.

Source: Table 14.3.2.5

Adverse Events by Severity

In both studies 3001 and 3002, the majority of TEAEs across treatment groups were reported as mild or moderate in severity (i.e., Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or Grade 2). In study 3001, 12.5% in the Ondibta arm and 13.5% in the EU Lantus arm experienced at least 1 Grade 3 TEAEs, and 4.9% in the Ondibta arm and 4.2% in the EU Lantus arm experienced at least 1 Grade 4 TEAEs. In study 3002, 6.4% in the Ondibta arm and 4.3% in the EU Lantus arm experienced at least one Grade 3 TEAE. One subject in the EU Lantus treatment group experienced a Grade 4 TEAE, and no Grade 5 TEAEs were reported in either treatment group.

2.5.8.3. Serious adverse event/deaths/other significant events

Study 3001:

Of 287 subjects treated with Ondibta, a total of 30 SAEs were reported in 10 (3.5%) subjects. Of 289 subjects treated with EU Lantus, a total of 26 SAEs were reported in 14 (4.8) subjects.

Table 33 Serious AEs by Preferred Term (Safety Analysis Set)

Category Preferred Term	GL Glargine Injection (N=287) [n (%) m]	EU Lantus (N=289) [n (%) m]
Any serious adverse event	10 (3.5) 30	14 (4.8) 26
Hypoglycaemia	3 (1.0) 20	1 (0.3) 1
Acute kidney injury	0	2 (0.7) 2

Table 33 Serious AEs by Preferred Term (Safety Analysis Set)

Category Preferred Term	GL Glargine Injection (N=287) [n (%) m]	EU Lantus (N=289) [n (%) m]
Depression	0	2 (0.7) 2
Hyperglycaemia	1 (0.3) 1	1 (0.3) 1
Appendicitis	0	1 (0.3) 1
Benign neoplasm of spinal cord	1 (0.3) 1	0
Carotid artery occlusion	1 (0.3) 1	0
Cellulitis	1 (0.3) 1	0
Cerebrovascular accident	0	1 (0.3) 1
Cough	0	1 (0.3) 1
Craniocerebral injury	0	1 (0.3) 1
Diabetic foot	1 (0.3) 1	0
Diabetic ketoacidosis	0	1 (0.3) 1
Endocarditis	0	1 (0.3) 1
Gangrene	1 (0.3) 1	0
Inguinal hernia	0	1 (0.3) 1
Localised infection	0	1 (0.3) 1
Lower limb fracture	1 (0.3) 1	0
Lumbar vertebral fracture	0	1 (0.3) 1
Metabolic acidosis	0	1 (0.3) 1
Osteomyelitis	0	1 (0.3) 1
Peripheral ischaemia	0	1 (0.3) 1
Peritonitis	0	1 (0.3) 1
Pneumonia	0	1 (0.3) 1
Post procedural infection	1 (0.3) 1	0
Prurigo	1 (0.3) 1	0
Rib fracture	0	1 (0.3) 1
Sepsis	0	1 (0.3) 2
Septic shock	0	1 (0.3) 1
Suicidal ideation	0	1 (0.3) 1

Table 33 Serious AEs by Preferred Term (Safety Analysis Set)

Category Preferred Term	GL Glargine Injection (N=287) [n (%) m]	EU Lantus (N=289) [n (%) m]
Thrombosis	1 (0.3) 1	0
Tibia fracture	0	1 (0.3) 1

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group; SAE=serious adverse event.

Note: AEs were coded using MedDRA Version 22.0. For each System Organ Class and Preferred Term, subjects are included only once, even if they experienced multiple events in that System Organ Class or Preferred Term.

One subject was reported with a hypoglycemia SAE with criteria of life threatening but with CTCAE Grade 3. Another subject had 2 hypoglycemia events reported as SAEs that were no longer considered SAEs after reevaluation by Investigator.

Source: Table 14.3.2.11

Study 3002:

Of 281 subjects treated with Ondibta and 282 subjects treated with EU Lantus, the percentage of subjects with at least 1 SAE was similar in the Ondibta (5.3%) and the EU Lantus treatment groups (5.7%) during the 26-week treatment period.

Table 2.7.4- 1: List SAEs by Preferred Term in Study 3002

Category Preferred Term	GL Glargine Injection (N=281) [n (%) m]	EU Lantus (N=282) [n (%) m]
Any serious adverse event	15 (5.3) 21	16 (5.7) 18
Chest pain	2 (0.7) 2	0
Non-cardiac chest pain	1 (0.4) 1	1 (0.4) 1
Osteomyelitis	2 (0.7) 2	0
Skin ulcer	1 (0.4) 1	0
Syncope	1 (0.4) 1	0
Angina pectoris	0	1 (0.4) 1
Angina unstable	1 (0.4) 1	0
Arthritis	1 (0.4) 1	0
B-cell small lymphocytic lymphoma	0	1 (0.4) 1
Back pain	1 (0.4) 1	0
Cardiac failure congestive	1 (0.4) 1	0
Cardiomyopathy	0	1 (0.4) 1
Carotid artery aneurysm	0	1 (0.4) 1
Cellulitis	1 (0.4) 1	0
Chronic lymphocytic leukaemia	0	1 (0.4) 1
Fall	1 (0.4) 1	0
Gastrointestinal haemorrhage	0	1 (0.4) 1
Hyperglycaemia	0	1 (0.4) 1
Hypertensive emergency	0	1 (0.4) 1
Infection	0	1 (0.4) 1
Intervertebral disc protrusion	0	1 (0.4) 1

Category Preferred Term	GL Glargine Injection (N=281) [n (%) m]	EU Lantus (N=282) [n (%) m]
Lactic acidosis	0	1 (0.4) 1
Localised infection	0	1 (0.4) 1
Osteoarthritis	1 (0.4) 2	0
Pancreatic carcinoma	1 (0.4) 1	0
Pancreatitis acute	1 (0.4) 1	0
Rectal haemorrhage	0	1 (0.4) 1
Renal cell carcinoma	0	1 (0.4) 1
Silent myocardial infarction	0	1 (0.4) 1
Spondylolisthesis	1 (0.4) 1	0
Transient ischaemic attack	0	1 (0.4) 1
Vertebral foraminal stenosis	1 (0.4) 1	0
Wound infection	0	1 (0.4) 1

(Source: Study GL-GLAT2-3002; Table: 14.3.2.11)

In study 3001, one death (sepsis) was reported in the EU Lantus treatment group. This event was not considered related to the study drug. There were no other deaths during the three studies.

2.5.8.4. Laboratory findings

For both haematology and clinical chemistry parameters, no substantial differences between treatment groups were observed in studies 3001 and 3002.

2.5.8.5. Immunological events

Immunogenicity

Study 1002

A single sample for determination of AIAs was taken pre-dose at baseline for potential analysis in case of safety concerns or PK/PD parameters. Of 40 (35.7%) subjects tested at baseline, 30 (75%) subjects were confirmed positive for AIAs, with a mean (SD) titer of 39.000±69.0597.

Study 3001

Samples for AIA assessments were collected at baseline, screening and pre-dose at Week 12 and at the end-of-treatment visit (week 26).

The primary immunogenicity endpoint of this study is percentage of subjects in each treatment group who developed treatment-induced AIA, defined as newly confirmed positive AIA development or important (at least a 4-fold) increase in titer, after baseline and up to visit Week 26.

The incidence of treatment-induced AIA up to Week 26 was similar between the Ondibta and EU Lantus treatment groups.

Statistical analysis showed that Ondibta was found similar in treatment-induced AIA to Lantus as the difference in proportions (difference [90% CIs (-5.4, 6.5)]) fell between the similarity margins (-11.3, 11.3) (Table 2.7.4-19).

Table 2.7.4- 2: Primary Analysis of the Incidence of Treatment-Induced AIA (Safety Analysis Set)

Time Point	Incidence of Treatment-Induced AIA [n (%)]		Treatment Difference (%) (ASE)a	90% Confidence Interval (%)	Similarity Marginb (%)
	GL Glargine Injection (N=287)	EU Lantus (N=289)			
Up to Week 12	61 (21.3)	54 (18.7)	-	-	-
Up to Week 26	74 (25.8)	73 (25.3)	0.6 (3.63)	(-5.4, 6.5)	(-11.3, 11.3)

AIA=anti-insulin antibodies; ASE=asymptotic standard error; EU Lantus=European Union-approved Lantus; GL Glargine Injection=Gan & Lee Insulin Glargine Injection; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group; SAP=statistical analysis plan.

[a] Differences in proportions and associated confidence intervals are from a logistic regression model adjusted by country and are presented for GL Glargine Injection group minus the EU Lantus treatment group. Missing outcomes are imputed using a treatment policy approach as described in Table 4 of the SAP Version 3 (Appendix 16.1.9).

[b] Similarity margins are prespecified in SAP Version 3, Table 3 (Appendix 16.1.9), which requires linear interpolations for values that fall between those tabulated reference AIA rates.

Source: Table 14.2.1.1.1

Study 3002

Samples for AIA assessments were collected at screening and pre-dose at Week 12 and at the end-of-treatment visit (Week 26).

The **primary immunogenicity endpoint** of this study is percentage of subjects in each treatment group who developed treatment-induced AIA, defined as newly confirmed positive AIA development or important (at least a 4-fold) increase in titer, after baseline and up to visit Week 26. Up to Week 12, 37 (13.2%) and 38 (13.5%) subjects showed treatment induced AIAs were found similar in the Ondibta and Lantus treatment groups, respectively. The incidence of treatment-induced AIA up to Week 26 was similar between the Ondibta and EU Lantus treatment groups. The percentages of subjects positive for treatment-induced AIA (composite of newly developed or important increase in AIA) up to Week 26 were similar between the Ondibta (19.2%) and EU Lantus (21.3%) treatment groups, with a 90% CI (-7.6, 3.5) of the difference in proportions (-2.1 percentage points) that fell completely between the similarity margins (-10.7, 10.7) for equivalence.

Of the subjects with confirmed positive AIA results after baseline, no subject in Ondibta treatment group and 3 subjects (18.8%) in the EU Lantus treatment group had developed anti-insulin NAbs up to Week 12. Up to Week 26, 1 subject (10.0%) in the Ondibta treatment group and 3 subjects (18.8%) in the EU Lantus treatment group had developed anti-insulin Nabs. The difference in proportions of subjects who developed anti-insulin NAbs up to Week 26 between the Ondibta and EU Lantus treatment groups was -8.7 percentage points (ASE: 13.61; 90% CI: -31.1, 13.6). As developed NAbs after baseline was low in both treatment groups, similarity across treatment groups was not concluded.

Table 2.7.4- 3: Analysis of the Incidence of Subjects with Neutralizing Antibodies (Safety Analysis Subset - Subjects with Confirmed Positive Anti-Insulin Antibodies after Baseline)

Time Point	Incidence of Neutralizing Antibodies after Baseline [n (%)]		Treatment Difference (%) (ASE)a	90% Confidence Interval (%)
	GL Glargine injection (N=10)	Lantus (N=16)		
Up to Week 12	0	3 (18.8)		
Up to Week 26	1 (10.0)	3 (18.8)	-8.7 (13.61)	(-31.1, 13.6)

AIA=anti-insulin antibodies; ASE=asymptotic standard error; EU Lantus=European Union-approved Lantus; GL Glargine injection=Gan & Lee Insulin Glargine injection; n=number of subjects in a treatment group in a category; N=number of subjects in a treatment group; NAb=neutralizing antibody; SAP=statistical analysis plan.
Note: Percentages are based on the number of subjects with confirmed positive AIA results after baseline and up to visit Week 26 as the denominator (SAPVersion 3, Section 6.3.1 [Appendix 16.1.9]). No imputation is applied.
a Differences in proportions and associated confidence intervals are from a logistic regression model and are presented for GL Glargine injection group minus the EU Lantus treatment group.
Source: Listing 16.2.8.5, Table 14.2.1.2.3

2.5.8.6. Discontinuation due to adverse events

The rate of discontinuation due to TEAEs in the Ondibta arms of studies 3001 (two subjects) and 3002 (one subject) was low and comparable between treatment arms.

2.5.8.7. Post marketing experience

The product has been marketed in China since 2005 with a reportedly favourable B/R profile.

2.5.9. Discussion on clinical safety

The safety results in this submission are presented for the pivotal PK/PD similarity study 1002 and for the two phase 3 studies. A total of 678 subjects received one or more doses of Ondibta. In study 3001 and 3002, the median treatment duration was 3.5 months (maximum 6.07 months), and this patient exposure is considered sufficient for a biosimilar application.

Being a biosimilar application, the safety assessment mainly focused on general adverse events (AEs), hypoglycaemia, and on a comparison to the reference product (EU Lantus) with respect to immunogenicity. With regard to hypoglycaemia, which is related to an exaggerated pharmacological effect, the demonstration of similar PK and PD profiles is key for providing reasonable reassurance that this adverse effect can be expected at similar frequencies.

The incidence of AEs overall was similar between Ondibta and EU Lantus; most AEs were hypoglycaemia. The rate of discontinuation due to TEAEs in study 3001 and 3002 was low and comparable between treatment arms. Overall, no new safety signals were identified in these studies.

In the single dose BE study 1002, the most common TEAEs were headache and hypoglycaemia. The frequency was comparable between treatment arms.

In studies 3001 and 3002, serious AEs were infrequent with both Ondibta and Lantus (incidences of approximately 4-6%) and only 4 subjects had serious adverse events of hypoglycaemia. Hypoglycaemia was the only AESI. A similar proportion of subjects experienced hypoglycaemic TEAEs in the phase three studies. The incidence of nocturnal hypoglycaemia in the phase 3 studies was similar between Ondibta and Lantus. The incidence of medical interventions of hypoglycaemia events in the Ondibta and EU Lantus groups were comparable.

With regard to immunogenicity, the incidence of AIAs seem comparable between Ondibta and EU Lantus. In both studies 3001 and 3002, the incidence of treatment-induced AIA (new AIA development or an at least 4-fold increase in titer between baseline and up to visit Week 26) was similar between the Ondibta and EU Lantus treatment groups. There are no signs of an impact of AIAs on safety of Ondibta.

The Applicant has provided new tables, in which the AEs are stratified also by treatment arms. Results are

provided for "hematology" and "clinical chemistry" parameters.

2.5.10. Conclusions on the clinical safety

From a safety perspective, the investigational programme supporting the present application is considered adequate. The patient exposure is considered sufficient for a biosimilar application, and no significant differences in the safety profiles between Ondibta and the comparator EU Lantus have been reported.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Medication errors due to mix-up between long-acting (basal) and short-acting (bolus) insulins
Important potential risks	Malignancies
Missing information	None

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Medication error due to mix-up between long-acting (basal) and short-acting (bolus) insulins	Routine risk communication: *SmPC: Section 4.2, 4.4 and 6.6* *PL: Section 3* Routine risk minimisation activities recommending specific clinical measures to address the risk: *SmPC: Insulin Glargine must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation is included in Section 4.2.* *Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins is included in Section 4.4 and 6.6.* *PL: Do not mix insulin glargine with any other insulins or medicines is included in Section 3.* Other routine risk minimisation measures beyond the Product Information:

	Prescription only medicine.
Malignancies	Routine risk communication: *SmPC: None* *PL: None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *SmPC: None* *PL: None* Other routine risk minimisation measures beyond the Product Information: *Prescription only medicine.*

2.6.4. Conclusion

RMP version 0.2 is considered 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

Product Information of Ondibta is aligned with Product Information of the reference procedure Lantus.

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the reference product Lantus (insulin glargine). 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, Ondibta (Insulin glargine) is included in the additional monitoring list as a biological 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

Claimed indication

Claimed indication of Ondibta is identical to the approved indication of the reference product Lantus (insulin glargine):

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

Quality aspects

The biosimilarity of Ondibta to the EU Lantus reference medicinal product was assessed using a range of state-of-the-art analytical tests in line with the EMA *Guideline on Similar Biological Medicinal Products containing Biotechnology-derived proteins as active substance* (EMA/CHMP/BWP/247713/2012).

Non-clinical aspects

The non-clinical programme aimed at proving similarity between Ondibta and EU approved Lantus primarily based on *in vitro* pharmacology studies in accordance with requirements presented in 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).

Additionally, a 4-week repeat-dose toxicity study in rats assessing systemic exposure and safety profile of insulin glargine for Ondibta and US Lantus at doses of up to 27.5 U/kg/day was conducted. However, *in vivo* animal studies are not deemed necessary for biosimilarity assessment of insulin in accordance with the guideline. Hence, the study is only considered supportive.

Clinical aspects

A hyperinsulinaemic clamp study was performed in order to establish biosimilarity. This approach follows 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).

Additionally, two phase 3 studies assessing efficacy and safety was performed. As those are not deemed necessary for a biosimilarity assessment of insulin, those studies are considered supportive only.

3.2. Results supporting biosimilarity

Quality aspects

Design of the biosimilarity exercise

Analytical similarity of Ondibta to the reference medicinal product (RMP), EU Lantus, was assessed in a comprehensive biosimilarity exercise performed in line with the relevant EU guideline on quality aspects of the development of similar biological medicinal products (EMA/CHMP/BWP/247713/2012).

Quality attributes (QAs) included in the biosimilarity exercise cover: protein content (assay and total protein), excipient content (zinc concentration), primary structure, disulfide linkage, secondary and higher-order structure, product-related substances and impurities (as assessed by multiple methods, including RP-HPLC, CEX-HPLC, HI-HPLC and LC-MS peptide mapping), and biological characteristics, i.e. target binding, phosphorylation, mitogenicity, and metabolic activity (glucose uptake, glycogen synthesis, lipogenesis). The set of QAs included in the biosimilarity exercise is considered appropriate.

The methods used for assessing the QAs were generally either fully validated or qualified.

For all quantitative QAs, mean ±X SD quality ranges (QRs) were calculated based on data for EU RMP lots. Consequently, in the current setting, the statistical approach based on QRs may be considered overall supportive and one part of the similarity assessment based on the totality of evidence. For non-quantitative QAs, a side-by-side comparison irrespective of the QA risk category was performed, which is considered acceptable.

Concerning the lots used in the biosimilarity exercise, for the test product, the selection of test lots and RMP lots to include in the biosimilarity exercise is considered acceptable. the number of lots tested, the spread of their expiry dates and ages, and the representation of data are considered acceptable for all QAs.

Three different reference standards (RSs) have been used during the biosimilarity exercise. Upon receiving the responses to the LoQ it has been informed which RS was used with which lot, and it has been clarified how replacement of one RS with another during the biosimilarity studies has been accounted for in the interpretation of the data**.**

Quality Attributes		Test Method	Whether Highly Similar [1]
Content	Assay	Reverse phase- high performance liquid chromatography (RP-HPLC)	Yes
	Total protein content		Yes
Primary structure and disulfide linkage	Intact molecular weight (MW) and reduced MW	Liquid chromatography-mass spectrometry (LC-MS)	Yes
	Peptide mapping and full-length sequencing	Liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry (LC-MS/MS)	Yes
	Disulfide linkage		Yes
		Nuclear magnetic resonance (NMR)	Yes
	Isoelectric point (pI)	iCIEF	Yes
	Far – UV CD	Circular dichroism (CD)	Yes

[1] "Yes" indicates that the results support the conclusion that GL Glargine Injection is highly similar to EU Lantus.
"Yes*" indicates that the results did not meet the similarity acceptance criteria. However, the differences observed do not preclude a demonstration of highly similar between GL Glargine Injection and EU Lantus, and justification is provided accordingly.

Quality Attributes		Test Method	Whether Highly Similar [1]
Secondary and higher order structure	Near – UV CD		
	Intrinsic fluorescence	Fluorescence spectrometry	Yes
	Alpha-helix	Fourier transform infrared spectrometer (FTIR)	Yes
	Beta-sheets		
	Beta-turns		
	Random coil		
	Oligomer MW	Non-denatured size exclusion chromatography multi-angle light scattering (N-SEC-MALS)	Yes
	Melting temperature	Differential scanning calorimetry (DSC)	Yes
	Hydrodynamic diameter	Dynamic light scattering (DLS)	Yes
Product related variants[2]	Deamidation	RP-HPLC	Yes
		Cation-exchange chromatography high performance liquid chromatography (CEX-HPLC)	Yes
	Mis-cleavage (C-terminal truncation of B-chain)	RP-HPLC	Yes
	Cysteine residue variants		Yes
		RP-HPLC& LC-MS	Yes
		Ellman’s assay	Yes
	Aggregates	Size exclusion-high performance liquid chromatography (SE-HPLC)	Yes*
	Mis-cleavage of N-terminal extension of A-chain & C-terminal truncation of B-chain	RP-HPLC	Yes

[2] During the characterization of EU Lantus and GL Insulin Glargine, a few impurities which were below LOQ of the method were also assessed, collected and identified as dehydration of mis-cleavage, fragment, acetylation, demethylation, esterification and propionylation.

Quality Attributes		Test Method	Whether Highly Similar [1]
	Carbamylation		Yes
	Oxidation, dehydration of mis-cleavage, fragment, acetylation, demethylation, propionylation and esterification		Yes
	Amino acid substitution	CEX-HPLC	Detected in GL Glargine Injection but not detected in EU Lantus by CEX-HPLC. Detailed characterization and investigation were conducted.
	Sum of acidic peaks and sum of basic peaks	CEX-HPLC	Yes
	Sum of hydrophobic peaks and sum of hydrophilic peaks	Hydrophobic interaction high performance liquid chromatography (HI-HPLC)	Yes
Related proteins	Total related proteins	RP-HPLC	Yes
	Maximum individual related protein		Yes
Excipient	Zinc content	Atomic adsorption spectroscopy (AAS)	Yes*
Target binding	IR-A binding	Surface plasmon resonance (SPR)	Yes
	IR-B binding		Yes
	IGF-1R binding		Yes
	IR-A phosphorylation	Cell based assay	Yes*

Quality Attributes		Test Method	Whether Highly Similar [1]
Receptor phosphorylation	IR-B phosphorylation		Yes
	IGF-1R phosphorylation		Yes
Mitogenic activity	IGF-1R-dependent mitogenicity	Cell based assay	Yes
	IR-dependent mitogenicity		Yes
Metabolic activity	Glucose uptake	Cell based assay	Yes*
	Glycogen synthesis		Yes
	Lipogenesis		Yes
In vitro potency		Cell based assay (In-cell western)	Yes

Comparative stability studies

Comparative stability studies were carried out on GL insuline glargine and EU Lantus to assess similarity in terms of degradation profiles. The studies were performed under accelerated conditions and stressed conditions, with the latter including: High temperature, low pH, high pH, oxidation, light exposure, and mechanical agitation.

Under accelerated conditions, Trends were otherwise similar. Under the stressed conditions, the trends were in most cases similar, although with some minor exceptions, which were however not considered concerning. Overall, the accelerated and forced degradation studies are considered supportive of a conclusion of biosimilarity.

Non-clinical aspects

The provided *in vitro* pharmacology studies showed adequate evidence of biosimilarity between Ondibta and the EU-approved reference product Lantus with respect to receptor binding affinity (IR-A, IR-B and IGF-1R), receptor phosphorylation (IR-A, IR-B and IGF-1R), metabolic activity (glucose uptake, glycogen formation and lipogenesis) and mitogenic potential (IGF-1R and IR-dependent). Additionally, biosimilarity was also seen for *in vitro* IR-B potency.

Based on a 4-week repeat-dose toxicity study in rats the assessment of systemic exposure and the safety profile of insulin glargine for Ondibta and US Lantus at doses of up to 27.5 U/kg/day can be considered comparable. Bioanalytical methods were adequately validated to support the bioanalysis of insulin glargine and anti-insulin glargine antibodies in the 4-week repeat-dose toxicology study in rats. In addition, method validation reports for the conducted *in vitro* pharmacology studies were submitted and assessed as part of the quality dossier and no concerns were identified.

Clinical aspects

PK/PD: In the pivotal PK/PD study GL-GLA-CT-1002, biosimilarity between Ondibta and EU Lantus was demonstrated for both PK ($AUC_{0\text{-}24h}$ and C_{max} of the insulin glargine M1) and PD ($AUC_{GIR.0\text{-}24h}$ and GIR_{max}). It was demonstrated by statistical analysis, ANOVA, that for both primary PK endpoints $AUC_{0\text{-}24h}$ and C_{max} of the insulin glargine M1 the similarity limits (90% CI of the geometric LS-mean treatment ratio within the limits 80.00–125.00%) were met. The results of the statistical analysis demonstrate that for both primary PD

endpoints $AUC_{GIR.0-24h}$ and GIR_{max} the similarity limits (95% CI of the LS-mean ratio of untransformed data of treatments within the limits 80.00-120.00%) were met.

Efficacy: The two phase 3 studies in type 1 and type 2 diabetes patients, respectively, showed non-inferiority of Ondibta in comparison with the reference product, Lantus, as the confidence intervals of the HbA_{1c} difference between the products did not reach the non-inferiority margin of 0.3%.

Safety: No significant differences in the safety profiles between Ondibta and the comparator EU Lantus have been reported. The rate of hypoglycaemia was comparable.

Immunogenicity: In both studies 3001 and 3002, the incidence of treatment-induced AIA (new AIA development or at least a 4-fold increase in titer between baseline and up to visit Week 26) was similar between the Ondibta arms and EU Lantus arms.

3.3. Uncertainties and limitations about biosimilarity

There are no remaining uncertainties and limitations that have an impact on the conclusion of biosimilarity.

3.4. Discussion on biosimilarity

Quality

The analytical biosimilarity exercise is generally supportive of a conclusion on biosimilarity. Points for clarification have been answered satisfactorily and the analytical biosimilarity exercise is considered supportive of a conclusion on biosimilarity.

Non-clinical aspects

From a non-clinical perspective, the provided *in vitro* pharmacology results generally support biosimilarity of Ondibta and the EU-approved Lantus in accordance with the guideline (EMEA/CHMP/ BMWP/32775/2005_Rev. 1).

Based on a 4-week repeat-dose toxicity study in rats the assessment of systemic exposure and the safety profile of insulin glargine for Ondibta and US Lantus at doses of up to 27.5 U/kg/day can be considered comparable. Bioanalytical methods were adequately validated to support the bioanalysis of insulin glargine and anti-insulin glargine antibodies in the 4-week repeat-dose toxicology study in rats. In addition, method validation reports for the conducted *in vitro* pharmacology studies were submitted and assessed as part of the quality dossier and no concerns were identified.

Clinical

The Applicant conducted three clinical studies to demonstrate that Ondibta has a comparable PK and PD profiles with the reference insulin glargine, EU Lantus.

The Applicant also conducted 2 phase 3 studies which are not considered the pivotal studies, but the results of the two studies in type 1 and type 2 diabetes patients demonstrated that Ondibta was non-inferior to Lantus after 26 weeks of treatment, which supports further the biosimilarity between Ondibta and Lantus.

The incidence of AEs overall was similar between Ondibta and EU Lantus. No new safety signals were identified.

Overall, the efficacy and safety data support biosimilarity.

Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Ondibta is considered biosimilar to Lantus. 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 Ondibta 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 Ondibta is favourable in the following indication:

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

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.