25 January 2018
EMA/119474/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Semglee

International non-proprietary name: insulin glargine

Procedure No. EMEA/H/C/004280/0000

Note

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

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List of abbreviations

AA	Amino acids
API	Active Pharmaceutical Ingredient
AS	Active substance
AUC	Area under the Curve
AUC0-24h	Area under the concentration-time curve from time 0 to 24 hours
AUC0-6h	Area under the concentration-time curve from time 0 to 6 hours
AUCGIR	Area under the glucose infusion time curve
AUCins	Area under the serum insulin concentration-time curve
Avg	Average
BG	Blood glucose
BLOQ	Below Limit of Quantitation
CD	Circular Dichroism
CHO	Chinese hamster ovary
CHO-IGF1R cells	CHO cells expressing recombinant human IGF1R
CHO-IR cells	CHO cells expressing recombinant human IR
CI	Confidence interval
CID	Charge Injection Device
cIEF	Capillary Iso-electric focusing
CIEX	Cation Exchange Chromatography
Cins.max	Maximum plasma insulin concentration
CL	Confidence limit
Cmax	Observed Maximum Concentration
CMC	Chemistry, Manufacturing, and Controls
CPPs	Critical process parameters
CV	column volume
CV	Coefficient of variation, expressed in percent
Da	Dalton
dL	Deciliter
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DO/DO2	Dissolved Oxygene
DoE	Design of experiments
DP	Drug Product
DS	Drug Substance
EC50	Half-maximal effective concentration
ELISA	Enzyme-linked Immunosorbent Assay
EU	European Union
EU-approved Lantus	Lantus approved for marketing in the European Union
EURP	European Union Reference Product
F	Female
FMEA	Failure modes and effects analysis
FP	Finished product
G	Gram
g/L	Gram/Liter
GCP	Good clinical practice

Geo Mean	Geometric mean value
GIR	Glucose infusion rate
GIRmax	Maximum glucose infusion rate
GLP	Good Laboratory Practice
GLUT4	Glucose transporter type 4
GM	Geometric mean
GSD	Geometric standard deviation
h	Hour
HCP	Host cell protein
HMWP	High Molecular Weight Protein
HPLC	High Pressure Liquid Chromatography
IC50	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEF	Iso-electric focusing
IGF1	Insulin-like growth factor 1
IGF1R	Insulin-like growth factor 1 receptor
IM	Intramuscular
IP	Intraperitoneal
IR	Insulin receptor
IR-A	Insulin receptor, isoform A
IR-B	Insulin receptor, isoform B
IU	International Unit
IV	Intravenous
KD	Equilibrium binding constant
kg	Kilogram
LC	Liquid Chromatography
LCL	Lower confidence limit
LC-MS	Liquid Chromatography Mass Spectrometry
LLOQ	Lower limit of quantification
M	Male
MAA	Marketing Authorisation Application
MCB	Master cell bank
mg	Milligram
mM	Millimolar
MS	Mass Spectroscopy
MS-MS	Tandem Mass Spectrometry
MTD	Maximum Tolerated Dose
N	Number of subjects or observations
N/A	Not applicable
NA	Not applicable
nM	Nanomolar
NOR	Normal operating ranges
PARs	Proven acceptable ranges
PD	Pharmacodynamics
pI	Isoelectric point
PFP	Pre-filled pen
PK	Pharmacokinetics

PO	Oral
rDNA	Recombinant Deoxyribonucleic Acid
RP	Relative potency
RP-HPLC	Reverse Phase - High Performance Liquid Chromatography
RS	Related Substance
RT	Retention Time
SC	Subcutaneous
SCP	Single Chain Precursor
SD	Standard Deviation
SEC-HPLC	Size-exclusion High Performance Liquid Chromatography
SMBG	Self-Monitoring of Blood Glucose
SPR	Surface Plasmon Resonance
t½	Terminal insulin half life
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TE	Trace Elements
tGIRmax	Time to maximum glucose infusion rate
Tmax	Time to reach Cmax
TV	Total variability
U	Unit
UCL	Upper confidence limit
US	United States
US-approved Lantus	Lantus approved for marketing in the USA
USRLD	United States Reference Listed Drug
UV	Ultraviolet
w/v	Weight/volume
WCB	Working Cell Bank
λz	Terminal elimination rate constant
µM	Micrometer

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 1 August 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Semglee, 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.

The legal basis for this application refers to:

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

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 Community provisions in force for not less than 6/10 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:
  - Community
- Community Marketing authorisation number: EU/1/00/134/001-037

Medicinal product authorised in the Community/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:
  - Community
- Community Marketing authorisation number: EU/1/00/134/001-037

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Lantus
- Marketing authorisation holder: Sanofi-Aventis Deutschland GmbH
- Date of authorisation: 09-06-2000
- Marketing authorisation granted by:
  - Community

- Community Marketing authorisation number(s): EU/1/00/134/001-037

Information on Paediatric requirements

Not applicable for biosimilar applications.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 March 2009 and 24 April 2014. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 1 August 2016.
- The procedure started on 27 October 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 January 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 30 January 2017
- During the meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 23 February 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 August 2017.
- The following GMP and GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection at 1 clinical site and 1 bioanalytical site in Germany between 23 January 2017 to 27 January 2017, and 7 February 2017 and 9 February 2017, respectively. The outcome of the inspection carried out was issued on 11 April 2017.
  - A GMP inspection at 1 manufacturing site in India between 13 March 2017 and 17 March 2017. The outcome of the inspection carried out was issued on 5 July 2017.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 September 2017.
- During the PRAC meeting on 28 September 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 12 October 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 December 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 10 January 2018.
- During the meeting on 25 January 2018, 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 Semglee.

2. Scientific discussion

2.1. Problem statement

The prevalence of diabetes across adults from 20 to 79 years in 2015 was estimated to be 8.8%, which represents 415 million people. In Europe, the prevalence of diabetes was estimated to be about 9.1%, and in North America (including the Caribbean), about 12.9%. Long acting insulin analogues are efficacious and offer glycemic control over 24 hours. Mylan's investigational drug product MYL 1501D was being developed as a proposed biosimilar product to Lantus licensed in the European Union (EU), hereafter referred to as Lantus-EU, and Lantus licensed in the United States, hereafter referred to as Lantus-US. In early studies, Lantus licensed in India (referred to Lantus-IN) was used as the reference product. The proposed indication is the same as that approved for Lantus, i.e., for the treatment of diabetes mellitus in adults and children over 2 years of age. Data submitted with the dossier contain analytical, non-clinical and clinical data aiming at establishing biosimilarity between MYL-1501D and EU-approved and US-licensed Lantus in terms of purity, safety, immunogenicity and efficacy and, hence, to demonstrate that there is no clinically meaningful difference between MYL-1501 D and Lantus.

About the product

Note: beside of the current product name Semglee, the previous names MYL-1501D, FFP-112, Mylan's Insulin Glargine, MIG and MYL IG is being used throughout this document.

Semglee has been developed to be a biosimilar product to Lantus. Semglee has the same amino acid sequence as Lantus and, in contrast to Lantus which is produced in *E. coli*, is produced in *Pichia pastoris* (ayeast).

Type of Application and aspects on development

This application is being made on the basis of Article 10(4) of EC Directive 2001/83/EC as biological medicinal product which is similar to a reference biological product. Comparability is being claimed with Lantus 100 units/mL (insulin glargine; 100 U/mL solution for injection in a cartridge) solution for injection

which was first authorised in the European Union on 09 June 2000 (MA number EU/1/00/134). The Marketing Authorization Holder is Sanofi-Aventis Deutschland GmbH.

The development programme (MYL-1501D) was designed to meet recommendations in the following EMA regulatory guidelines on biosimilars:

-Guideline on similar biological medicinal products (CHMP/437/04), 2005

-Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005), 2005; and revision (EMEA/CHMP/BMWP/42832/2005 Rev1), 2014.

-Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMEA/CHMP/BWP/49348/2005), 2006

- 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), 2015.

Annex to guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: Non-clinical and clinical issues, (EMEA/CHMP/BMWP/32775/2005), 2006, and revision (EMEA/CHMP/BMWP/32775/2005_Rev. 1), 2015.

The programme was also designed to comply with Scientific Advice from the EMA provided previously.

2.2. Quality aspects

2.2.1. Introduction

Semglee (insulin glargine), also referred to as MYL-1501D, has been developed to be a biosimilar product to Lantus (reference medicinal product).

The finished product is presented as a solution for injection in a pre-filled pen (PFP) containing 100 units/mL of insulin glargine equivalent to 3.64 mg/mL. The excipients are: metacresol, glycerol, Zinc chloride, Hydrochloric acid/Sodium hydroxide for pH adjustment and water for injections (WfI). The quantitative and qualitative composition of Semglee is the same as the formulation of the reference product Lantus presented in cartridge/pre-filled pens.

The product is available in Type I colourless glass cartridge with a plunger (bromobutyl rubber), sealed using lined seals (laminate of polyisoprene and bromobutyl rubber). The cartridge is assembled in a disposable pen injector. Each pre-filled pen contains 3 ml of solution and comes in packs of 1, 3, 5 pens.

The disposable pen injector with integrated 3 mL glass cartridges is intended for subcutaneous administration of the product.

2.2.2. Active Substance

General information

The active substance, recombinant insulin glargine, is a structurally modified insulin analogue. Semglee has the same amino acid sequence as Lantus and, in contrast to Lantus which is produced in *E. coli*, is

produced in *Pichia pastoris* (a yeast). The C-terminal end of the B-chain is elongated by two arginine residues and the C-terminal asparagine of the A-chain is replaced by glycine.

Manufacture, characterisation and process controls

Origin, source and history of cell line development

The active substance is expressed as a recombinant precursor protein in the host *Pichia pastoris* (a yeast).

A two tiered cell bank system, comprising master cell bank (MCB) and working cell bank (WCB) was established. Adequate release specifications and characterisation data of MCB and WCB were provided; a protocol for future establishment of new WCBs was provided as well.

End-of-production and post-production cell banks (the latter with additional cell generations after end of production) were established and their testing provided evidence of genetic stability during the entire production time. All raw materials are controlled by adequate specifications.

Description of manufacturing process and process controls

The illustration and description of the manufacturing process presented is complete and very detailed. It includes the manufacture in a production fermenter by a fed-batch process, followed by purification of the precursor protein from the harvest culture supernatant. The final MYL-1501D is purified through an enzymatic cleavage step in combination with a series of filtration and chromatography steps.

The process is designed to remove impurities including the process-related Pichia-specific glycosylated variants. Excipients are added to generate the formulated active substance.

Appropriate hold times have been established for process intermediates and for several processing solutions.

The active substance manufacturing process has been extensively and adequately described.

Control of critical steps and intermediates

The process has been developed based on prior knowledge from development gained from other insulin products. For critical process parameters normal operating ranges (NORs) have been defined. Based on process characterisation studies proven acceptable ranges (PARs) were also defined. Respective study reports were provided to support the PARs. Based on the study reports provided, the classification of process controls according to criticality is considered acceptable.

Process validation

A process validation study has been conducted with batches manufactured at commercial scale according to the NORs that have been defined. Process characterisation studies were also performed. They included a failure modes and effects analysis (FMEA) evaluation, subsequent studies of selected parameters for their impact on process performance and critical quality attributes and presentation of PARs derived thereof in addition to the NORs. The process characterisation studies provided evidence for representativeness of small scale studies for the commercial scale and justification for the PARs derived thereof.

Clearance of process- and product-related impurities has only been presented based on real time results of the process verification batches. While for the enzyme used to cleave the precursor protein adequate removal could be demonstrated by data, removal capacities for host DNA and host cell protein (HCP) cannot be derived due to the low levels found. However, testing for both residuals is included in the active substance specification and this is considered to be acceptable.

Hold time studies were performed for all intermediates intended to be held for a certain processing time and the hold times are considered supported.

Tabulated results of lifetime studies for chromatography resins have been provided on a concurrent basis at commercial scale. Additional data has been provided to define sufficient column performance.

Manufacturing process development

Process development was initially driven by prior knowledge from manufacture of other insulin products. Further process development aimed at the improvement of operability, productivity, quality, scale-up, and adapting the process to different facilities. Several active substance manufacturing processes have been utilised throughout the development.

Process comparison and comparative in-process data were provided to support similarity of different processes. In addition, a detailed product comparability study was provided to also support comparability of the resulting active substances from different processes. With a view to the biosimilarity claim the intended commercial process was developed aiming to reduce glycosylated product-related variants not contained in the reference product by improving the clearance capability of downstream chromatography steps for these impurities. Moreover, the scale was further increased and manufacture was transferred were a sufficient number of product consistency runs and process verification runs were manufactured. The comparability of active substances is considered supported by the data provided. Development of the process is overall described with sufficient detail.

Characterisation

Characterisation studies have been performed using representative MYL-1501D active substance (AS) and finished product (FP) batches. The AS batches have been manufactured using the intended commercial active substance manufacturing process.

The primary, secondary and tertiary structures have been found comparable to the profiles of EU and US Lantus reference. Identical amino acid sequence of both chains, an accurate molecular mass for the intact protein as well as for the two chains A and B, a similar distribution of the disulphide bridges as well as comparable secondary and tertiary structure profiles could be confirmed for all batches tested. Non-reduced peptide mass fingerprint used for evaluation of the correct formation of disulphide bridges revealed two additional peaks which have been identified to be undigested insulin glargine structures.

Several analytical methods have been used for control of MYL-1501D active substance impurity profile and are considered adequate for characterization and control of impurities including RP-HPLC and SEC-HPLC. The capability and suitability of the proposed analytical methods to resolve and differentiate between glycosylated and non-glycosylated impurities/species has been demonstrated.

Biological activity has been investigated using several *in vitro* assay methods for evaluating the metabolic, mitogenic, insulin receptor binding, IGF-1 receptor binding and insulin receptor phosphorylation activity. Additionally, the *in vivo* assay described in the Pharmacopoeia was carried out

to demonstrate the biological activity of MYL-1501D. Forced degradation studies revealing significant photo degradation as well as degradation under acidic and oxidative conditions have been presented.

Specification

Adequate active substance specifications have been provided comprising identity testing and impurity testing.

Residual host cell protein determination and host cell DNA determination are performed using adequate assays. In addition, contents of zinc, as well as residual solvents are tested at active substance release and during stability, as appropriate. Likewise, loss on drying, sulphated ash as well as endotoxins and microbial limits are controlled at active substance release and during stability. In general, the proposed specification is considered adequate.

The proposed impurity ("Related Compounds") specification including both limits for glycosylated impurities and for other impurities is considered acceptable. The specification contains a limit for glycosylated variants to guarantee very low levels of these variants in future batches.

The general approach to justify the proposed specifications taking into consideration process batch data as well as stability data is considered adequate. Based on this, the proposed acceptance limits for the specified parameters seem reasonably deduced.

Analytical methods

Most of the analytical procedures applied for control of the active substance are in-house methods for which acceptable descriptions have been provided. In light of the current Ph. Eur. Monograph "Insulin glargine" the company's in-house analytical methods are justified as being more suitable and discriminating than the pharmacopoeial ones. This is considered acceptable. In addition, a cell-line and process-specific ELISA is proposed for determination of *Pichia pastoris* host cell proteins (HCP). The new test has been demonstrated to be suitable for the intended purpose. Sufficient details have been provided with regard to the validation of the proposed analytical procedures included in the AS specification. The proposed in-house analytical procedures were demonstrated to meet the pre-defined validation requirements.

Batch analysis

Batch data have been provided for active substance batches used in the pre-clinical and clinical development, process validation and stability batches. All batches comply with the specifications in place.

Reference standard

Sufficient details have been provided on the reference standard system established for active substance manufacture. Working reference standards are used. Qualification of the previously and currently used standards is considered adequate. An appropriate qualification protocol for future reference standards has been provided.

Container Closure

Sufficient detail on the container used for storage of the AS has been provided.

Stability

Stability data have been provided for commercial active substance batches stored for up to 6 months at the proposed long-term storage condition and for up to 6 months at accelerated conditions. In addition, long-term stability data are available from supporting batches stored up to 48 months.

All the batch data comply with the pre-determined active substance specifications. Based on the data, the claimed active substance shelf life is supported. The proposed stability protocol containing adequate stability-indicating test parameters is considered appropriate.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

MYL-1501D finished product (Semglee) is a clear, colourless liquid supplied in a pre-filled pen (PFP) intended for subcutaneous administration. The disposable pen injector with integrated 3 mL glass cartridges is sealed with a polyisoprene/bromobutyl seal and closed with a bromobutyl rubber stopper. The cartridges are filled with a nominal volume of 3.0 mL. It contains 100 units/mL of insulin glargine equivalent to 3.64 mg/mL. Apart from insulin glargine as the active substance, Semglee contains the preservative metacresol; glycerol as a tonicity agent; Zinc chloride as stabiliser and Hydrochloric acid/Sodium hydroxide for pH adjustment in water for injections (WfI) (adjusted to target pH). The quantitative and qualitative composition of Semglee is the same as the formulation of the reference product Lantus presented in cartridge/pre-filled pens.

Pharmaceutical development

Semglee formulation was developed in several stages and characterisation studies were conducted with the formulation selected for commercial manufacture were used to further support the finished product composition and to study the tolerance ranges in the concentrations of the excipients in terms of the finished product stability. For these studies an appropriate design of experiments (DoE) concept was applied. Based on the results, the qualitative and quantitative composition of Semglee is regarded adequate with regard to product quality and stability.

The manufacturing process of Semglee has been appropriately developed. Process development studies were conducted at the laboratory scale to study the impact of critical parameters on product stability. Process characterization studies were used to identify critical process parameters and to evaluate acceptable input parameter ranges and normal operating ranges of variables to be used during routine manufacturing operations and are confirmed to be adequate to ensure consistent product quality. In the course of the manufacturing process development the finished product production was transferred to the final commercial manufacturing site. The transfer involved an increase in the FP batch size and changes in the equipment. Analytical comparability between the finished product of these two production sites was appropriately evaluated and confirmed. Semglee finished product batches manufactured at the commercial manufacturing site by using active substance of the commercial AS process showed a lower level of impurities/product-related substances when compared with finished product manufactured during development.

Compatibility of the container closure system with MYL-1501D FP was sufficiently evaluated by extractable and leachable (E&L) studies. Potential leachables and extractables of the primary container closure components have been evaluated in extensive studies.

In conclusion, the compatibility of the selected primary packaging components with Semglee formulation has been appropriately demonstrated. Container closure integrity is routinely controlled at finished product batch release and during stability studies.

Antimicrobial efficacy of the preservative was tested at the end of in-use stability studies. The efficacy of the preservative was also demonstrated at its lower acceptance limit of 80% of the label claim.

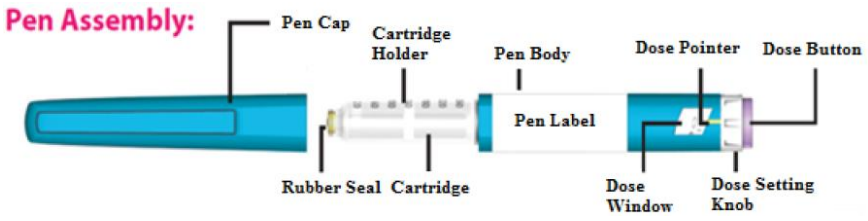
Medical Device

The manufacturers of the pen components and subassemblies are EN ISO 13485:2012 certified and comply with requirements for design, development and manufacture of "Disposable Pen Injectors". Evidence has been provided that Semglee disposable pen injector fulfils the essential requirements of the EU Medical Device Directive.

Specifications for the pen body sub-assembly have been presented. The final commercial pen configuration was verified in view of accuracy and robustness apart from other aspects by considering the relevant ISO standards on pen injector systems. A selection of commercially available needles was applied in these studies and confirmed to comply with the requirements. The needle sizes compatible with the Semglee pen injector are indicated in the Instructions for Use.

Human Factor Validation and clinical evaluation studies were conducted in order to confirm that Semglee pen injector and the Instructions for Use are appropriate for use by the intended user population.

Figure 2: Representative diagram of MYL-1501D finished product presented as Pre-filled Pen (PFP)



Manufacture of the product and process controls

The cartridge manufacturing process has been sufficiently described. The batch formula of a commercial batch has been adequately presented.

The process starts by mixing the active substance with the first set of excipients. Subsequently the remaining excipients are added. The pH is adjusted to target and the volume is made up to 100%. The bulk solution is filtered into a sterile vessel. Final sterile filtration is carried out on-line and the filtered solution is filled into the sterile cartridges and closed. The primary packaging components are sterilized at the finished product manufacturing site prior to use.

Process parameters applied for operating the manufacture of MYL-1501D FP cartridges are indicated. Critical process parameters (CPPs) have been described. The target set points and ranges of the CPPs are within the ranges evaluated during process development.

The manufacturing process is controlled by appropriate in-process controls (IPC). Process verification was achieved by manufacturing several consecutive full-scale cartridge validation batches at the commercial manufacturing site. The testing programme, the sampling plan and the number of samples taken were acceptable. During the validation runs all process parameters were kept within their acceptable ranges or met the target value. Process validation was completed by testing several batches according to the release specification. All parameters tested met their acceptance criteria. No trend was observed even when multiple samples had been taken and analysed. The results confirm that the cartridge manufacturing process at the commercial manufacturing site consistently produces Semglee cartridges of the intended quality.

Results of the filter validation studies involved the evaluation of filter compatibility and bacterial retaining capacity in the presence of the finished product as well as extractables and leachables from the filter materials.

The pen assembly process has also been depicted and described. Checks after each step of the assembly process assure the correct assembly of the disposable pen. For the purpose of pen assembly process validation, a sufficient number of consecutive pen injector batches were manufactured at the commercial site. In addition, supportive validation data from a sufficient number of consecutive pen injector batches have been presented which are assessed supportive since they were manufactured by an assembly process demonstrated to be comparable. All results met the acceptance criteria. Although the size of the validation batches was significantly lower than the intended commercial batch scale the total data presented are considered sufficient to give assurance on the consistency of the assembly process. Adequate evidence that the assembly process does not impact the physicochemical and microbiological quality of the finished product was also provided.

Product specification

The list of test parameters for the finished product specifications contains tests on identity, Zn content, impurities, assay, pharmaceutical characteristics and cartridge function and dimension. The analytical methods are correctly assigned to the test parameters. Furthermore, shelf-life specifications are proposed for stability indicating parameters.

Specific compounds were detected in the finished product formulation not detectable in the active substance. These substances were adequately identified and characterized. The level of these compounds in finished product batches was found to be low. For all other impurities, a comparison between the amounts found in Semglee solution and the corresponding active substance batches demonstrated that there is no considerable increase during the finished product manufacturing process.

A risk assessment of the elemental impurities in MYL-1501D finished product in accordance with ICH Q3D has been presented. Analysis of Semglee finished product confirmed that none of the potential elements is above its limit of quantification in the finished product solution.

The specified acceptance range for Zn amount, insulin glargine content, the pharmaceutical attributes as well as the performance and functional properties of the pen have been adequately justified and are accepted. The approach for the justification of the specification limits of the impurities is acceptable. In addition, the proposed pen specification is considered adequate.

Analytical methods

The analytical methods have been described in sufficient detail. The non-compendial methods used for routine control were adequately validated.

Batch analysis

Batch analysis data have been presented for a sufficient number of batches manufactured at the commercial manufacturing site using active substance of the intended active substance manufacturing process. All parameters complied with their acceptance criteria. The release results of the assembled pen confirmed conformance with the pen release specification.

Stability of the product

Stability studies on Semglee have been conducted in accordance to ICH requirements. A sufficient number of finished product batches have been included. Stability data up to 36 months were submitted for supporting batches. Up to 6 month's data has been provided for commercial scale FP. The stability testing programme followed the established specification. All test parameters tested complied with their acceptance criteria when Semglee cartridges were stored at the recommended storage condition up to 36 months.

In-use stability of cartridges was tested after assembly with the pen. All test results were within the acceptance criteria and confirmed adequate physicochemical and microbiological quality after 28 days of storage at 30°C.

Forced degradation studies at different stress conditions (temperature, light exposure, oxidation, pH and mechanical stress) revealed that the degradation rate is very similar between the FP samples deriving from different AS processes as well as in US and EU Lantus batches. Thus, it is considered justified to establish FP shelf life on the stability data of the previous FP batches. The claimed shelf life for the finished product of 24 months at the recommended storage temperature (2°C-8°C) is acceptable. After first use of the pen and based on the in-use stability results the product may be stored for a maximum of 4 weeks not above 30°C. Pens in use must not be stored in the refrigerator.

Biosimilarity

An extensive biosimilarity exercise was conducted to demonstrate analytical similarity of the test product MYL1501D with the reference product Lantus approved in the EU. In addition, analytical bridging was performed to compare the proposed biosimilar MYL1501D with EU and US Lantus.

Multiple MYL1501D FP batches containing active substance manufactured by an earlier manufacturing process as well as a sufficient number of finished product batches containing active substance manufactured by the intended commercialization process have been included in the similarity assessment. Furthermore, a sufficient number of EU and US Lantus batches were used as reference product.

In general, the choice of the test and reference product batches seems appropriate with regard to the number of batches, representativeness and differences in age. Analytical similarity study was performed by both, "side-by-side testing" as well as "stand-alone analyses". It has been clarified that the same analytical methods were used in case of "stand-alone" analyses although the tests were performed at different time points.

For the similarity study, quality attributes of insulin glargine were identified that may have impact on safety and efficacy. The quality attributes have been ranked and categorized for their criticality by applying risk assessment principles and tools in accordance with ICH Q8 and ICH Q9. Product variants such as size-, sequence-, pI- and deamidation- variants, product attributes comprising protein content, amino acid sequence, higher order structure and zinc content and functional attributes determined as metabolic and mitogenic activity have been evaluated for analytical similarity between the test and reference product.

Biological activity in terms of *in vitro* metabolic and *in vitro* mitogenic activity as well as *in vivo* (USP rabbit bioassay) was also investigated. Comparable biological activity against the insulin receptor (both IR-B and IR-A) and the insulin growth factor with regard of binding and auto-phosphorylation activity could be demonstrated for the MYL1501D test product, EU Lantus and US Lantus. Likewise, glucose uptake activity, cell proliferation and rabbit bioassay potency was found similar between the test and the reference product and the comparator.

Structural comparability between the MYL1501D test product and the EU Lantus reference product and the comparator US Lantus was studied by applying numerous state-of-the-art methods demonstrating similarity in terms of primary (i.e., amino acid sequence), secondary, tertiary structure and molecular mass.

Purity and impurity of MYL1501D test product, EU Lantus and US Lantus has been assessed both with regard to HMWP content and product variants (by RP-HPLC).

Determination of HMW proteins using SEC-HPLC as well as orthogonal analytical methods (SEC-MALS and AUC) substantiated that HMW proteins of the test product are consistently below the values found for the reference product EU Lantus and the comparator US Lantus.

Comparison of product variants/impurities between test and reference product is considered acceptable. Presence of product variants/impurities in the reference product have been appropriately addressed and compared between test and reference product.

Deamidation/clipped species were present in comparable amounts in both, the test and the EU reference product. Product related impurities such as conjugates are lower in MYL1501D test product than in EU Lantus and US Lantus.

Regarding the analytical similarity with respect to zinc content, the applicant has appropriately justified and demonstrated the analytical similarity with Lantus EU.

A straight-forward statistical approach was used to assess the analytical similarity.

With respect to glycosylated impurities, the active substance manufacturing process has been substantially improved to reduce glycosylated species. Furthermore, acceptable measures have been implemented to control the residual low levels of glycosylated impurities at active substance release. Consequently, similarity between the proposed test and reference products can be supported and the claim of analytical similarity between the MYL1501D test product and the EU Lantus reference product as well as bridging between EU Lantus and US Lantus is considered adequate.

The outcome of the physicochemical and biological comparability exercise between MYL-1501D and Lantus is summarised in the table below.

Table 5: Physico-chemical methods used to characterize and compare MYL-1501D and Lantus

Structural Characteristics	Attributes	Methods	Key findings
Primary Structure	Amino Acid Sequence	Reduced Peptide Mass Finger Printing (MS)	Identical amino acid sequence
		Intact Mass	Comparable mass
		Mass of A & B chains	Comparable mass
Secondary and Higher Order Structure	Protein Conformation	Far UV circular dichroism	Comparable secondary structure
		Fourier Transform infrared spectroscopy (FTIR)	Comparable higher order structure
		Disulfide Bridging (non-reduced peptide mass finger printing (MS)	The fragments obtained after digestion under non-reducing conditions show comparable masses which confirm the identical nature of the disulfide linkages.
		Confirmation of disulfide bridge by 2D NMR	Confirmation of disulfide linkage between A6-A11, A7-B7 and A20-B19
		Near UV circular dichroism	Comparable higher order structure
		Differential scanning calorimetry	Comparable melting temperature (Tm)
		Intrinsic Fluorescence	Comparable higher order structure
		Extrinsic Fluorescence	Comparable higher order structure
		X-ray crystallography	Identical three dimensional structure
Protein content	Content	RP-HPLC assay	Comparable protein content
Iso-electric point	pI	cIEF	Comparable iso-electric point (pI)
Impurities and Variants	Impurities (acetylation, deamidation, conjugation) Glycosylated variants	RP-HPLC	Comparable levels of impurities Glycosylated variants not present in the reference product and at or below limit of quantification for Semglee
Aggregates	High molecular weight impurities	Size Exclusion chromatography-UV	Comparable levels of aggregates
		Analytical ultracentrifugation (AUC)	Comparable sedimentation coefficient
		Size Exclusion chromatography-MALS	Comparable size range and distribution of molar mass
Excipient (Zn^{+2})	Zn^{+2}	Atomic absorption Spectroscopy	Comparable level of Zinc

Adventitious agents

Only animal origin-free materials were procured for cell banking and manufacture of the active substance. Research cell bank (the source of MCB) was checked for bacteria, yeast and mould contaminants.

Furthermore, unlike mammalian cell lines, yeast cell culture is not susceptible to transmit viral adventitious agents. Hence the risk of contamination with adventitious agents is very low.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Development, characterisation, manufacture and control of insulin glargine active substance and MYL-1501D finished product (Semglee) have been adequately described. EU GMP certificates have been issued for the active substance and finished product cartridge manufacturing sites as well as for the Semglee pre-filled pen assembly site.

The proposed active substance specification includes the requested limits for glycosylated variants. Semglee finished product has an identical composition as the reference product Lantus. Appropriate studies were conducted to further support the quantitative composition of the finished product and the selected finished product manufacturing process. The commercial manufacture of Semglee cartridge has been sufficiently described, controlled and verified to ensure a consistent production of the intended quality of Semglee cartridges. The proposed control of impurities/product-related substances in Semglee finished product at release and during the stability studies is acceptable. Finished product stability studies were adequately performed and the results support the shelf life claimed for Semglee.

Semglee pen injector was confirmed to deliver Semglee product accurately and safely. It was further demonstrated that the commercial assembly process consistently manufactures Semglee pre-filled pen of intended quality and performance. The assembly process does not compromise cartridge integrity and hence does not impact Semglee finished product quality.

For insulin glargine (Semglee) an extensive analytical similarity study has been conducted to compare insulin glargine manufactured in Pichia pastoris with Lantus reference product manufactured in E.coli. The active substance manufacturing process is capable to reduce glycosylated species and since acceptable measures of control have been implemented to control the remaining low levels of glycosylated impurities the similarity claim between the proposed test and reference products is justified. The claim of analytical similarity between the MYL1501D test product and the reference product Lantus approved in the EU as well as bridging between EU Lantus and US Lantus is supported.

2.2.5. 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. Biosimilarity to the reference product Lantus has been satisfactorily demonstrated at the quality level.

2.2.6. Recommendations for future quality development

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

2.3. Non-clinical aspects

2.3.1. Pharmacology

The applicant has covered all levels of comparison as required by the CHMP biosimilar insulin guideline, i.e. receptor binding, receptor activation (measured as autophosphorylation) and metabolic effects (glucose uptake, adipogenesis and inhibition of lipolysis). As requested by the guideline, these tests were performed in vitro since thereby a higher accuracy can be achieved than in vivo. Nevertheless, in-vivo studies were also presented. Furthermore, the applicant studied off-target binding to the IFG-1 receptor (IGF1R) and consecutive mitogenesis. The pharmacological studies performed are listed in the table below.

The evaluation of the study results is not fully in line with the European biosimilarity guideline. The applicant did not compare Glargine Mylan and the reference product Lantus directly, i.e. head-to-head in one experiment. Instead, each batch of Glargine Mylan and Lantus tested was compared to an internal working standard, and potency was calculated relative to this standard using a parallel line analysis. All comparisons were done at the level of relative potency values. On request the applicant provided all raw data, presented as concentration-response relationship curves so that plausibility of the calculated potency values could be assessed. The complete concentration-relationship curves provided much more information than the single potency value; the shape, steepness and upper limit of the curve are not reflected in the potency value. In most cases the individual data points fitted well to the expected sigmoid curve shape, indicating that a suitable concentration range was selected and that the results are reliable.

The following table provides an overview of the submitted studies.

Table: Compilation of the submitted PD studies

Type of Study	**Study ID**	**Test System/ Species, Strain**	**Mylan Formu-lation**
in vitro			
Insulin receptor long form (IR-B) binding affinity assay	U-15309	In vitro (Biacore)	
Insulin receptor short form (IR-A) binding affinity assay	U-15325	In vitro (Biacore)	
Total insulin receptor phosphorylation assay	TR002 (MQR001)	HepG2 cell line	
Insulin receptor-A phosphorylation assay	TR002 (MQR004)	CHO-K1 cells overexpressing IR-A receptors	
Insulin receptor-B phosphorylation assay	TR002 (MQR005)	CHO-K1 cells overexpressing IR-B receptors	
Metabolic bioassay: Long-term glucose uptake	TR002 (MQR003)	3T3-L1 cell line	
Metabolic bioassay: Adipogensis	RPT-MBN-007	3T3-L1 cell line	
Metabolic bioassay: Inhibition of lipolysis	RPT-MBN-010	3T3-L1 cell line	
in vivo			
Quantitative rabbit blood sugar assays	BIO-BA3319 and others	Rabbit, New Zealand White	D
Biological potency assay	N045	Mouse, Swiss Albino	A

In vivo pharmacodynamic study	BIO027	Mouse, Swiss Albino	A
secondary PD			
IGF-1 receptor binding affinity	TR002 (MQR002)	In vitro (Biacore)	
Mitogenic bioassay	TR002 (MQR006)	Saos-2 cell line	

Formulation D is identical to EU-Lantus;
Formulation A contains additional polysorbate-20 and differs in the concentration of the glycerol stock solution used for the preparation. Overall glycerol content remains unchanged.

In vitro studies

The results of the in-vitro studies were presented as concentration-response relationships which allow assessment of the biological plausibility of the results. In most cases data of test and reference product were compared art the level of relative potency. Concentration-response data were analysed using Parallel Line Analysis (PLA) software. The relative potency was obtained by calculating the linear portion of the dose response curve and comparing the ratio between the adjacent doses and the common slopes of any test agent (Lantus-EU, Lantus-US or MYL-1501D) to that of the internal working standard. In the respective figures below, the data corresponding to this standard are labelled in black.

Binding to IR-B including binding kinetics

Study U-15309

A surface plasmon resonance (SPR) based assay was used to evaluate the binding of insulin glargine to purified recombinant insulin receptors (IR-A and IR-B) in a Biacore instrument platform. The truncated, His-tagged receptor protein was immobilized on the surface of the CM5 sensor chip and the analyte (i.e. insulin glargine) was passed across the surface. Receptor protein (IR-A or IR-B) was coupled to the CM-5 binding surface by first washing the cells with EDC/NHS followed by a 6 µg/mL injection of the protein. The receptor protein was immobilized on the CM5 chip in 10 mM acetate buffer to a baseline of 1500 RU. The concentrations of glargine used ranged from 3.125 to 100 nM.

In generating the SPR data curves, Mylan's analysis method set curve fitting parameters were to a single model demonstrating reasonable fit and kinetic values with no adjustment or alteration of the curve fit between experiment/analyte/batch. The selected Langmuir model assumes 1:1 binding, first order kinetics, and equivalent but independent binding sites.

For determination of the association and dissociation rate (ka and kd) the measured curves (unsmooth colour lines in the figure below) were fitted to the above-mentioned function, and the black lines represent the fitted function. However, the fitted functions do not match the data curves very well. This may indicate that the binding and dissociation reactions did not follow the simple assumptions which were made by the applicant. On the other hand, a more complex model would likely introduce additional variability and/or bias to the data so that the applicant's approach is considered appropriate.

The figure below shows representative sensorgrams for the different glargine concentrations used, one sensorgram for comparator EU-Lantus (left) and one for the biosimilar product Glargine Mylan (MYL1501D, right).

It is likely that the calculated K_D values are too small (i.e. affinity of glargine to the receptor is overestimated) because association appears more slowly and dissociation faster with the raw data than with the fitted curve. However, the figure also shows that the deviation of the fit from the raw data is qualitatively and quantitatively similar in all three glargine preparations tested. Thus, this is no concern in respect to biosimilarity of the products. The shape of the curves meets the expectations, indicating that the results are plausible. No relevant differences between the three test products become obvious.

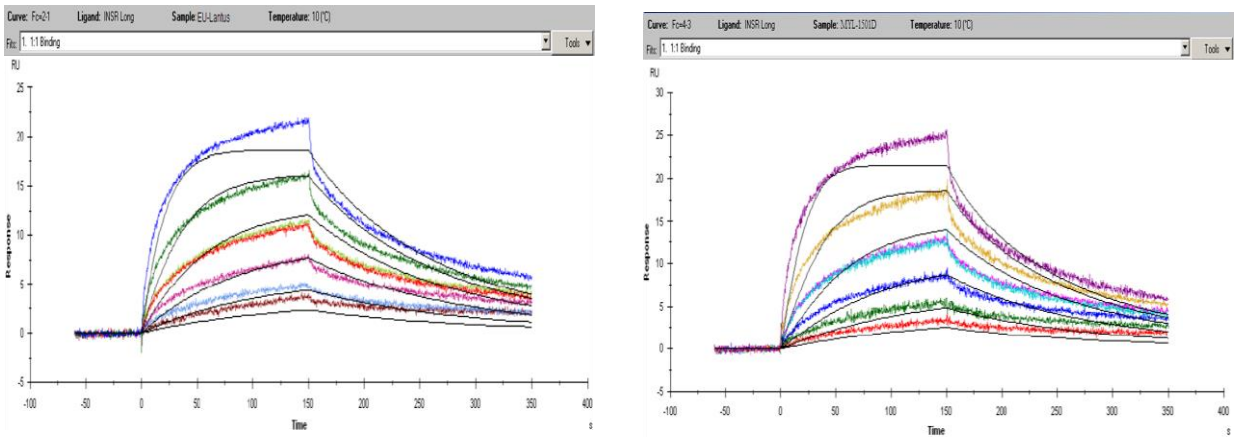


Figure: Representative Sensorgrams of Insulin Receptor (Long Form) binding Kinetic for EU-approved Lantus (left) and MYL-1501D (right). In each panel, the coloured lines correspond to the ascending glargine concentrations used, 3.125, 6.25, 12.5, 25 (twice), 50, and 100 nM.

The following table shows the calculated values for ka, kd and KD as mean and SD from all lots tested for Lantus EU, Lantus US and Glargine Mylan (MYL-1501D); multiple lots of each product were tested in three replicates each. No relevant differences between the three test products become obvious.

Table: Insulin Receptor (Long Form) binding kinetic constants for EU-Lantus, US-Lantus and MYL1501D

	Avg ka (1/Ms)	Avg kd (1/s)	Avg KD (nM)
Lantus EU			
Mean of Lantus Lots (Mean R)	7.06E+05	0.012	17.01
Standard Deviation of Lantus Lots (σR)	3.83E+04	0.001	0.94
Lantus US			
Mean of Lantus Lots (Mean R)	7.12E+05	0.013	17.68
Standard Deviation of Lantus Lots (σR)	3.14E+04	0.001	2.02
MYL-1501D			
Mean of MYL1501D Lots	7.09E+05	0.012	17.11
Standard Deviation of MYL1501D Lots	3.93E+04	0.001	0.76

Binding to IR-A including binding kinetics

Study U-15325

The ligand was Human insulin receptor (IR) protein (short isoform, extracellular domain, His tag). Experimental procedures were as described above for IR-B.

The figure below shows representative sensorgrams for the different glargine concentrations used, one sensorgram for comparator EU-Lantus (left) and one for the biosimilar product Glargine Mylan (MYL1501D, right). The shape of the curves meets the expectations, indicating that the results are plausible. No relevant differences between Lantus and MYL1501D become obvious.

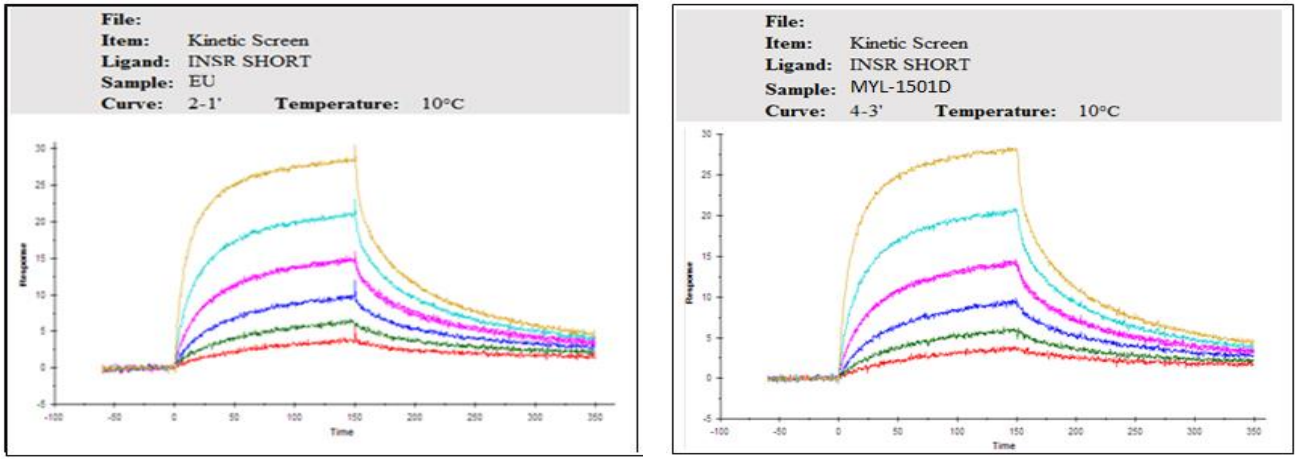


Figure: Representative Sensorgram for Insulin Receptor (Short Form) binding Kinetic with EU-approved Lantus (left) and MYL1501D (right)

The following table shows the calculated values for ka, kd and KD as mean and SD from all lots tested for Lantus EU, Lantus US and Glargine Mylan (MYL-1501D); multiple lots of each product were tested in three replicates each. No relevant differences between the three test products become obvious.

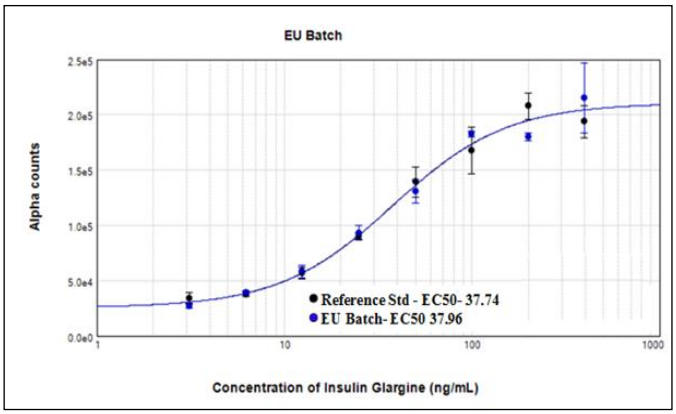
Table: Insulin Receptor (Short Form) binding kinetic constants for EU-Lantus, US-Lantus and MYL1501D

	Avg ka (1/Ms)	Avg kd (1/s)	Avg KD (nM)
Lantus EU			
Mean of Lantus Lots (Mean R)	1.45E+06	0.030	20.64
Standard Deviation of Lantus Lots (σR)	1.09E+05	0.005	2.26
Lantus US			
Mean of Lantus Lots (Mean R)	1.51E+06	0.030	19.87
Standard Deviation of Lantus Lots (σR)	1.70E+05	0.004	1.83
MYL-1501D			
Mean of MYL1501D Lots	1.56E+06	0.033	21.38
Standard Deviation of MYL1501D Lots	1.67E+05	0.005	1.72

Autophosphorylation of IR-B

CHO (Chinese hamster ovary) cells expressing IR-B were incubated with the test substances and lysed thereafter with the lysis buffer of the Alphascreen detection kit. The AlphaScreen Surefire technology was used for the detection of phosphorylated Insulin receptor in cellular lysate. Two antibodies recognize the phospho-Tyr 1150/1151 epitope and a distal epitope on Insulin receptor, respectively, and form a sandwich antibody complex. This complex is captured by AlphaScreen donor and acceptor beads, bringing them into close proximity. The excitation of the donor bead triggers emission of light at 520-620nm.

The figures below show a representative concentration-response curve of IR-B autophosphorylation for EU-Lantus (left) and Glargine Mylan (right). The data points do not show large variability and can easily be fitted to a sigmoid curve, indicating plausibility of the results.



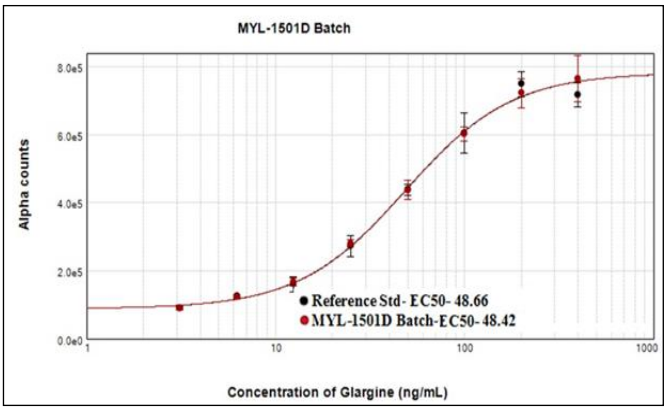


Figure: 4-PL Complete dose response curve representation for Insulin Receptor-B Phosphorylation Assay for EU-approved Lantus. The black line and symbols represent the internal standard. Left panel, Lantus; right panel, MYL1501D

The results of all batches tested for each test product (EU-Lantus, US-Lantus and MYL1501D) are summarised in the following table. Data are expressed as means and SD of potency relative to an internal standard (black line and symbols in the figure above). No relevant differences in relative potency between the three test substances (Lantus-EU, Lantus-US and Glargine Mylan) became obvious.

Table: Relative potencies of insulin receptor-B phosphorylation for EU-Lantus, US-Lantus and MYL1501D, expressed as means (SD) of all lots tested

Lantus EU Lots	1.06 (0.07)
Lantus US Lots	1.07 (0.06)
Mean of MYL1501D Lots	1.10 (0.07)

Autophosphorylation of IR-A

CHO cells expressing IR-A were used. Experimental procedures were the same as described above for IR-B.

The figures below show a representative concentration-response curve of IR autophosphorylation for EU-Lantus (left) and Glargine Mylan (right). The data points do not show large variability and can easily be fitted to a sigmoid curve, indicating plausibility of the results.

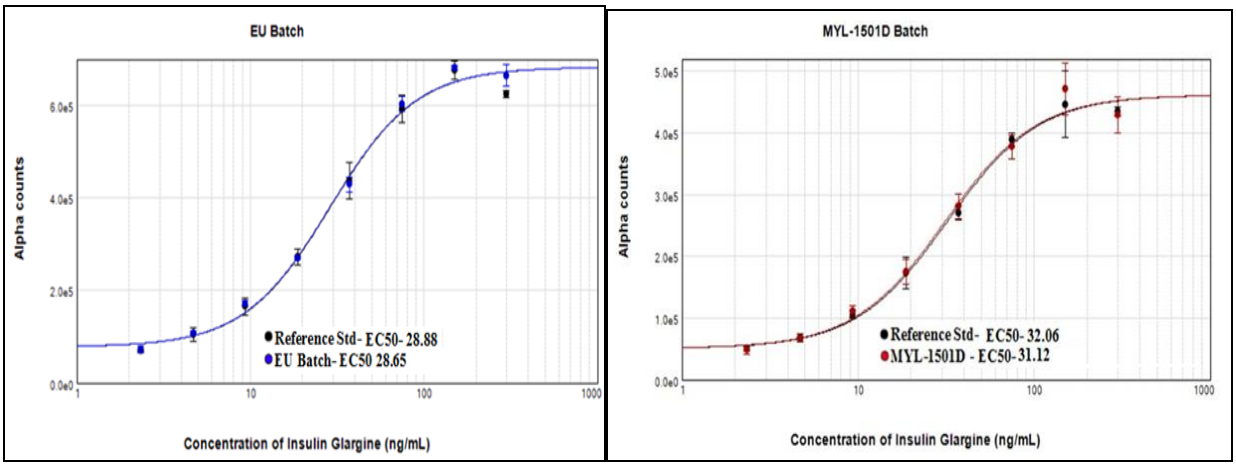


Figure: 4-PL Complete dose response curve representation for Insulin Receptor-A Phosphorylation Assay for EU-approved Lantus. Left panel, Lantus; right panel, MYL1501D

The results of all batches tested for each test product (EU-Lantus, US-Lantus and MYL1501D) are summarised in the following table. Data are expressed as means and SD of potency relative to an internal standard (black line and symbols in the figure above). No relevant differences in relative potency between the three test substances (Lantus-EU, Lantus-US and Glargine Mylan) became apparent.

Table: Relative potencies of insulin receptor-A phosphorylation for EU-Lantus, US-Lantus and MYL1501D, expressed as means (SD) of all lots tested

Lantus EU Lots	1.02 (0.09)
Lantus US Lots	1.06 (0.06)
Mean of MYL1501D Lots	1.06 (0.08)

Autophosphorylation of total IR in HepG2 cells

HepG2 hepatoma cells were used. Experimental procedures were the same as described above for CHO-IR-B cells.

The figures below show a representative concentration-response curve of IR autophosphorylation for EU-Lantus (left) and Glargine Mylan (right). The data points do not show large variability and can easily be fitted to a sigmoid curve, indicating plausibility of the results. Although the shape of the curve looks somewhat different for Lantus and Glargine Mylan, it should be noted that the curves of the test products (blue and red lines/symbols) are very close to the respective curves of the internal standard (black lines/symbols) to which the relative potency was referred.

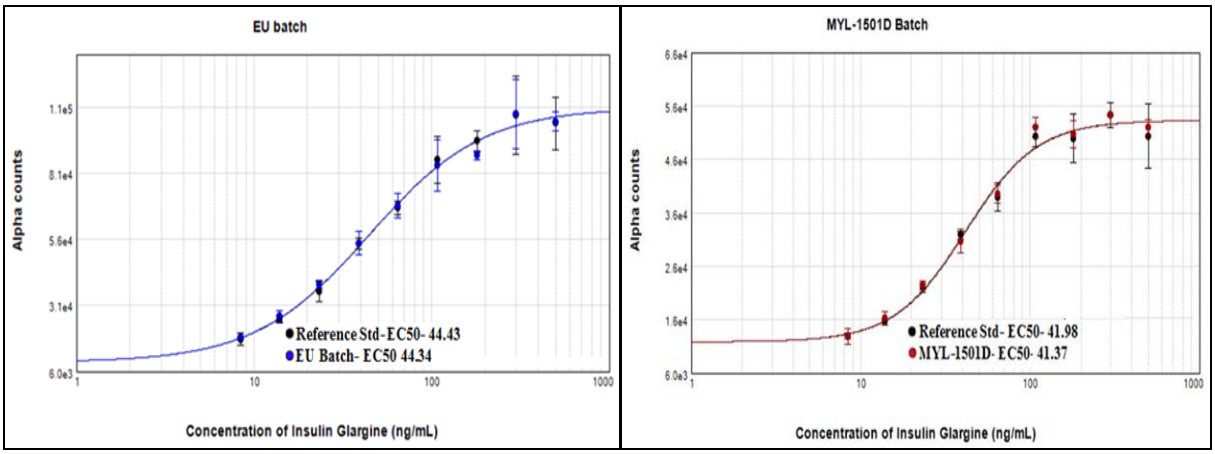


Figure: 4-PL Complete dose response curve representation for Insulin receptor (IR) as expressed in HepG2 cells. Left panel, Lantus; right panel, MYL1501D

The results of all batches tested for each test product (EU-Lantus batches, US-Lantus batches and MYL1501D batches) are summarised in the following table. Data are expressed as means and SD of potency relative to an internal standard (black line and symbols in the figure above). No relevant differences in relative potency between the three test substances (Lantus-EU, Lantus-US and Glargine Mylan) became apparent.

Table: Relative potencies of total insulin receptor phosphorylation in HepG2 cells for EU-Lantus, US-Lantus and MYL1501D, expressed as means (SD) of all lots tested

Lantus EU Lots	1.02 (0.07)
Lantus US Lots	1.03 (0.08)
Mean of MYL1501D Lots	1.04 (0.08)

Glucose uptake (long-term)

The method of determining glucose uptake used by the applicant is unusual. It measures the decrease of glucose concentration in the cell culture medium, assuming that glucose concentration decreases because the cells have consumed the glucose. Although this assumption is of course true, glucose consumption depends on many parameters and is not directly related to IR-mediated glucose uptake. In particular, measuring decreasing glucose in the medium requires rather long incubation of the cells with the test substances (22 h here) in order to achieve measurable differences. Insulin action over this time not only affects glucose uptake via GLUT4 but can also influence gene expression, cell proliferation or carbon hydrate and lipid metabolism in general. Hence, the response is very complex. In particular, an increased cellular glucose demand because of e.g. proliferation could result in insulin-independent glucose uptake. Thus, this assay would measure any ill-defined net insulin effect but not specifically glucose uptake via the insulin-sensitive transporter GLUT4 as desired. Therefore, glucose uptake is usually measured over short periods only (e.g. 15 min), and not glucose itself but a derivate that is recognised by GLUT4 and cannot be metabolised (2-deoxglucose) is used.

The relative potencies in respect to insulin-dependent glucose consumption as described above of MYL-1501D, Lantus-EU, and Lantus-US were highly similar (values ranged from 0.90 to 1.06, 0.83 to 1.12, and 0.94 to 1.12 respectively).

The response towards glargine was compared to the effect of another growth factor, VEGF (vascular endothelial growth factor). The latter had essentially no effect as desired.

The figures below show a representative concentration-response curve of glucose consumption for EU-Lantus (left) and Glargine Mylan (right). The data points do not show large variability and can easily be fitted to a sigmoid curve, indicating plausibility of the results. Although the shape of the curve looks different for Lantus and Glargine Mylan, it should be noted that the curves of the test products (blue and red lines/symbols) are very close to the respective curves of the internal standard (black lines/symbols) to which the relative potency was referred in each experiment.

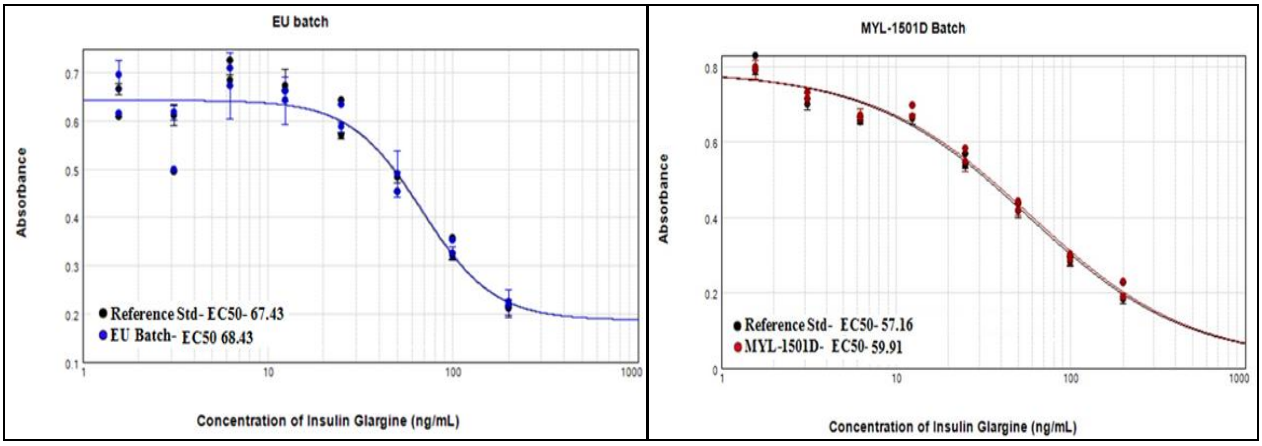


Figure: 4-PL Complete dose response curve representation for long-term glucose uptake for EU-Lantus (left) and MYL1501D (right)

The results of all batches tested for each test product are summarised in the following table. Data are expressed as means and SD of potency relative to an internal standard (black line and symbols in the figure above). No relevant differences in relative potency between the three test substances (Lantus-EU, Lantus-US and Glargine Mylan) became apparent.

Table: Relative potencies of long-term glucose uptake for EU-Lantus, US-Lantus and MYL1501D, expressed as means (SD) of all lots tested

Lantus EU Lots	1.01 (0.09)
Lantus US Lots	1.04 (0.06)
Mean of MYL1501D Lots	0.97 (0.05)

Adipogenesis

Insulin is an adipogenic hormone that triggers the differentiation of pre-adipocytes into mature adipocytes in a process known as adipogenesis. The initial step of this protocol was the culture of 3T3-L1 cells to 60-70% confluence. Differentiation was initiated by switching the cells to differentiation medium containing IBMX and ascending concentrations of insulin glargine, ranging from 0.79 to 12000 ng/mL. The cells were then incubated for six days. Thereafter, lipids were extracted and quantified by a fluorescence assay. The relative potency vs standard was calculated using SoftMax Pro 5.4.1 software.

The figures below show a representative concentration-response curve of adipogenesis for EU-Lantus (left) and Glargine Mylan (right). The data points do not show large variability and can easily be fitted to a sigmoid curve, indicating plausibility of the results.

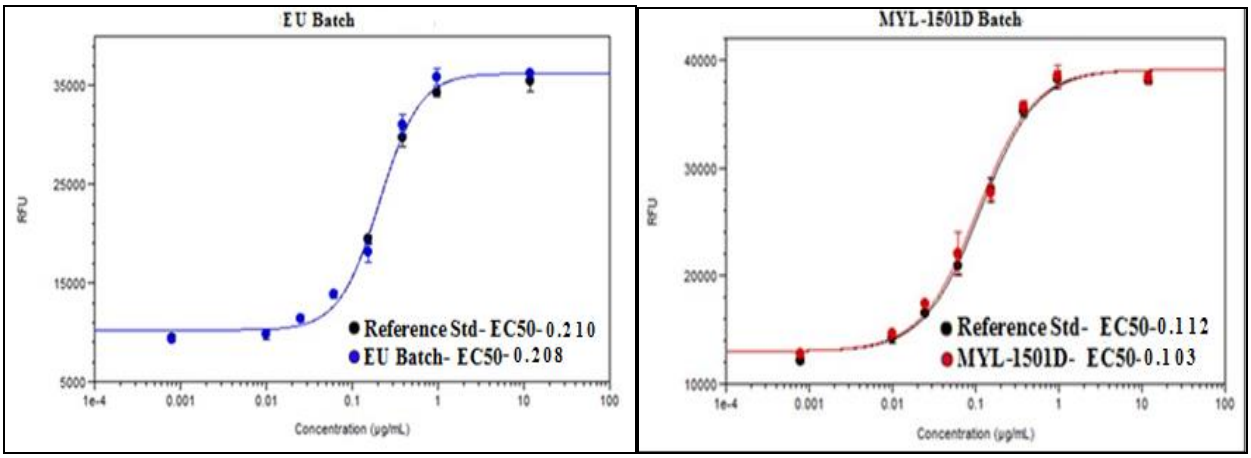


Figure: 4-PL Complete dose response curve representation in Softmax Pro for Adipogenesis Assay for EU-approved Lantus (left) and MYL1501D (right)

The results of all batches tested for each test product are summarised in the following table. Data are expressed as means and SD of potency relative to an internal standard (black line and symbols in the figure above). No relevant differences in relative potency between the three test substances (Lantus-EU, Lantus-US and Glargine Mylan) became obvious. Notably, the standard deviations of this functional assay were markedly larger than for the binding and autophosphorylation assays. Functional assays are testing more complex cellular functions than binding and phosphorylation assays do. Therefore, a higher degree of variability is expected is not of concern.

Table: Relative potencies of adipogenesis for EU-Lantus, US-Lantus and MYL1501D, expressed as means (SD) of all lots tested

Lantus EU Lots	1.06 (0.25)
Lantus US Lots	1.12 (0.29)
Mean of MYL1501D Lots	0.97 (0.12)

Inhibition of lipolysis

In an in vitro setting with 3T3-L1 cells, insulin inhibits adipolysis/lipolysis in a dose dependent manner. Lipolysis was measured by quantification of the free fatty acid released from the cells. The 3T3-L1 cells were differentiated by adding IBMX, dexamethasone, insulin and rosiglitazone to the culture medium. Lipolysis was stimulated with 3 nM of isoproterenol for 2 hours in the presence of ascending concentrations of insulin glargine (Lantus EU, Lantus US or Glargine Mylan). Supernatant was collected and a photometric free fatty acid assay was performed and evaluated by measuring absorbance at 570nm.

The figures below show a representative concentration-response curve of adipogenesis for EU-Lantus (left) and Glargine Mylan (right). The data points do not show large variability and can easily be fitted to a sigmoid curve, indicating plausibility of the results.

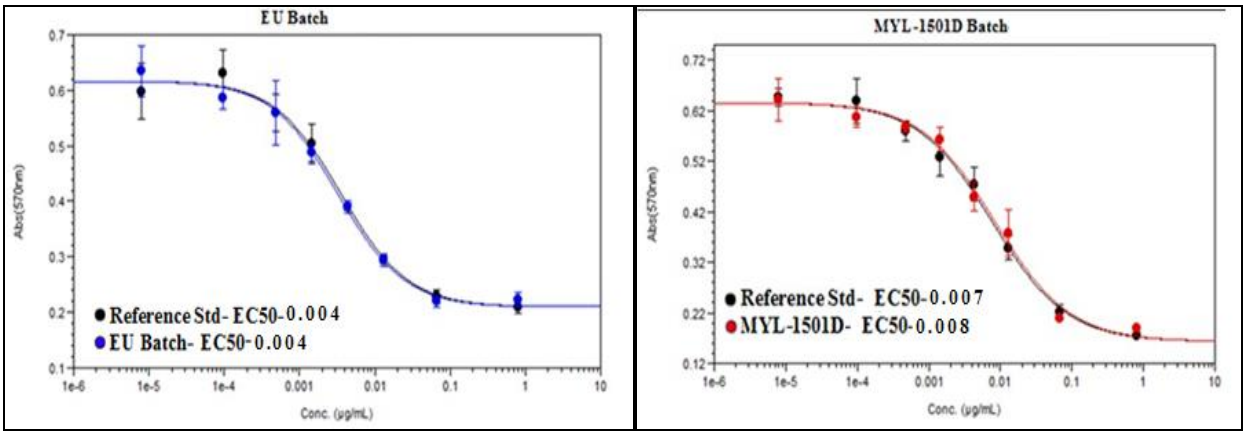


Figure: 4-PL Complete dose response curve representation in Softmax Pro for Inhibition of Stimulated Lipolysis Assay for EU-approved Lantus

The results of all batches tested for each test product are summarised in the following table. Data are expressed as means and SD of potency relative to an internal standard (black line and symbols in the figure above). No relevant differences in relative potency between the three test substances (Lantus-EU, Lantus-US and Glargine Mylan) became obvious. Notably, the standard deviations of this functional assay were markedly larger than for the binding and autophosphorylation assays. Functional assays are testing more complex cellular functions than binding and phosphorylation assays do. Therefore, a higher degree of variability is expected is not of concern.

Table: Relative potencies of lipolysis inhibition for EU-Lantus, US-Lantus and MYL1501D, expressed as means (SD) of all lots tested

Lantus EU Lots	0.84 (0.18)
Lantus US Lots	0.93 (0.31)
Mean of MYL1501D Lots	1.05 (0.20)

IGF1 receptor (IGF1R) binding

The experimental procedures were the same as described above for IR-B binding and kinetics (Study U-15309) except for the temperature during binding and dissociation. For IGF1R it was 25°C whereas the tests with IR-A and IR-B were performed at 10°C. Hence, binding and dissociation was faster with IGF1R.

The figure below shows the Biacore readout for two exemplary experiments, one for EU-Lantus and the other for Glargine Mylan.

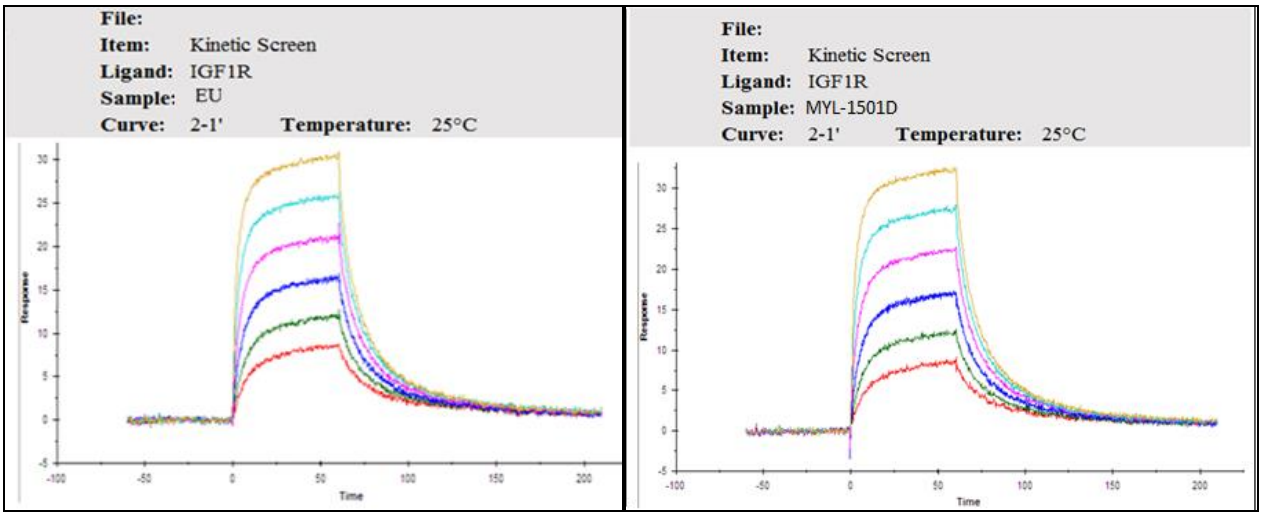


Figure: Representative Sensorgram of IGF-1R binding Kinetic with EU-Lantus (left) and MYL-1501D (right)

The following table shows the calculated values for ka, kd and KD as mean and SD from all lots tested for Lantus EU, Lantus US and Glargine Mylan (MYL-1501D); multiple lots of each product were tested in three replicates each. No relevant differences between the three test products became apparent.

Table: IGF1 receptor binding kinetic constants for EU-Lantus, US-Lantus and MYL1501D

	Avg k_a (1/Ms)	Avg kd (1/s)	Avg K_D (nM)
Lantus EU			
Mean of Lantus Lots (Mean R)	1.69E+05	0.04847	0.29
Standard Deviation of Lantus Lots (σR)	1.41E+04	0.00176	0.03
Lantus US			
Mean of Lantus Lots (Mean R)	1.71E+05	0.04954	0.29
Standard Deviation of Lantus Lots (σR)	1.14E+04	0.00201	0.02
MYL-1501D			
Mean of MYL1501D Lots	1.61E+05	0.048	0.30
Standard Deviation of MYL1501D Lots	7.04E+03	0.001	0.02

Mitogenesis

To compare the mitogenic potency of MYL-1501D with that of Lantus-EU and Lantus-US, Saos-2 human osteosarcoma cells were exposed to different batches and concentrations of the test articles, and proliferation was measured colourimetrically using the redox indicator dye Alamar Blue. Mitogenic potency was expressed relative to the working standard.

The response towards glargine was compared to the effect of another growth factor, VEGF (vascular endothelial growth factor). VEGF had no effect as desired.

The figures below show a representative concentration-response curve of mitogenesis for EU-Lantus (left) and Glargine Mylan (right). The data points do not show large variability and can easily be fitted to a sigmoid curve, indicating plausibility of the results.

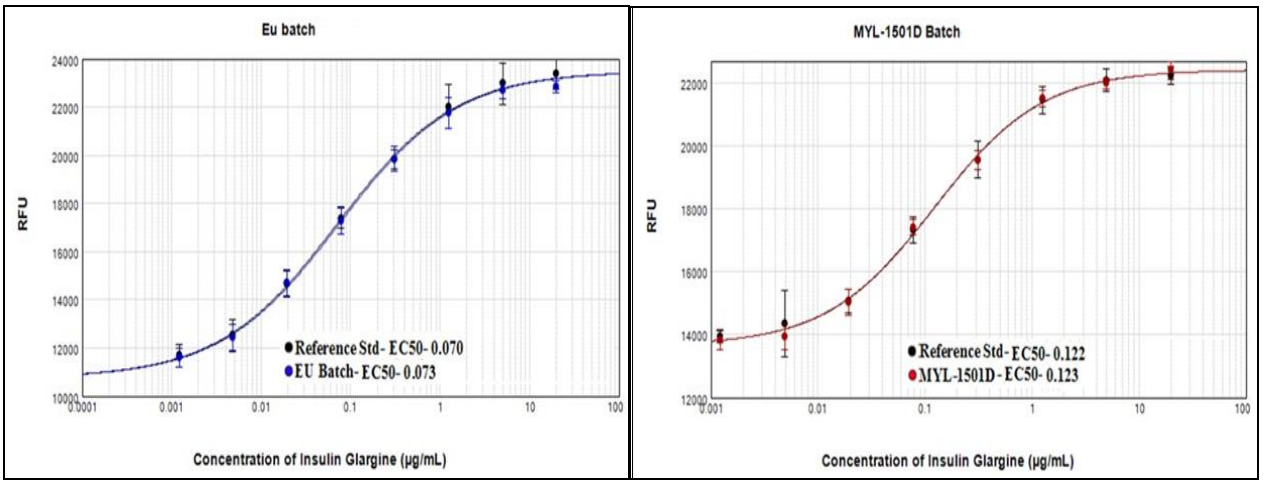


Figure: 4-PL Complete dose response curve representation for Mitogenic Assay for EU-approved Lantus (left) and MYL1501D (right)

The following table shows the calculated values for ka, kd and KD as mean and SD from all lots tested for Lantus EU, Lantus US and Glargine Mylan (MYL-1501D). No relevant differences between the three test products become obvious.

Table: Relative potencies of mitogenesis for EU-Lantus, US-Lantus and MYL1501D, expressed as means (SD) of all lots tested

Lantus EU Lots	1.02 (0.07)
Lantus US Lots	1.03 (0.10)
Mean of MYL1501D Lots	1.01 (0.07)

In vivo studies

Two studies in mice were performed, one with SC and one with IV insulin injection. The results of these studies show that Glargine Mylan and Lantus dose-dependently decreased blood glucose. The effect size was similar, but, as expected, the variability was large. Hence, in-vivo PD studies are not requested as part of the biosimilarity exercise.

2.3.2. Pharmacokinetics

No dedicated nonclinical pharmacokinetic studies were conducted for MYL-1501D. Toxicokinetic measurements were made in the repeat-dose toxicity studies (see respective section below).

2.3.3. Toxicology

An overview of the submitted toxicology studies is provided in the following table.

Table: Compilation of the submitted toxicology studies

Study ID	Species	Route	Doses	Animals per group	Duration	Comparator	GLP Y/N
Acute toxicity studies							
G4705	Mouse (Swiss albino)	SC	0-0.1-0.3-1 mg/kg (Formulation A)	5M,5F	N/A	None	Y
G4666	Rat (Wistar)	SC	0-0.18-0.6-1.8 mg/kg	5M,5F	N/A	None	Y

			(Formulation A)				
N0108	Rabbit (New Zealand White)	SC	0.009, 0.018, 0.045, 0.09 mg/kg Glargine Mylan, 0.045 mg/kg Lantus		N/A	Lantus-IN	N
Repeat-dose studies							
G11066	Rat (Wistar)	SC	0.08, 0.16, 0.38 mg/kg (Formulation C)	10M,10F	28-day, 14 days recovery	Lantus EU and US	Y
G4668	Rat (Wistar)	SC	0.03, 0.07, 0.15 mg/kg (Formulation A)	15M,15F; recovery 10M,10F; TK 6M,6F	90-day, 14 and 28 days recovery	Lantus-India	Y
G4669	Rabbit (New Zealand White)	SC	0.009, 0.018, 0.045 mg/kg (Formulation A)	4M,4F	90-day	None	Y
U16176	Rat (Wistar)	SC	MYL-1501D different manufacturing processes 0.08, 0.16, or 0.38 mg/kg	10M,10F; recovery 10M,10F; TK 9M,9F	28 days, 14 days recovery	Lantus-US	Y
Skin sensitisation test							
G4706	Guinea pig	intradermal	10 U		N/A	None	Y

Formulations A and C slightly differ from the formulation intended for marketing. Formulations C and the formulation intended for marketing are quantitatively identical in composition. They differ only in the concentration of the glycerol stock solution used for the preparation. Formulation A contains additional polysorbate-20. These differences are not considered toxicologically relevant.

In the **single-dose** studies, an expected dose-dependent decrease in blood glucose was observed. A comparator was not tested. No unexpected toxicity became obvious what is reassuring. However, a drug formulation was used (Formulation A) which is not intended for marketing. Furthermore, it is not clear whether the drug substance material used in these older studies is representative for the material intended for commercialisation.

Repeated-dose studies:

Study G11066: Comparative 28-Day Toxicity Study of MYL-1501D, Lantus-US and Lantus-EU Administered by Subcutaneous Route to Wistar Rats

Two *mortalities* occurred, 1 female in the MYL-1501D high-dose recovery group and 1 female in the Lantus-US high-dose group. No mortalities were observed in female rats in the Lantus-EU high-dose group.

Clinical signs of mild injury and scab formation at the injection site were observed in the in a few animals (some were in the placebo control group), mostly in Weeks 2 through 3. These clinical signs at the injection site were correlated with observations of reddish discoloration in gross pathology and haemorrhage, inflammation, and fibrosis in histopathology. Because no dose-dependent relationship was observed, the findings were attributed to the low pH of the formulation and to the injection procedure, rather than to the test or reference items per se. The signs generally appeared to have reversed by week 4 of the treatment period.

Functional observational tests were conducted in the control groups and the high-dose groups during week 4 of the treatment period. No abnormalities attributable to treatment were found.

Food intake and *body weight* were comparable among groups; some isolated changes in food intake were observed in some groups at certain time points but there was no general trend.

Expected treatment-related reductions in *plasma glucose* concentration (measured at study days 1 and 28) were observed, and they were approximately proportional to dose.

Toxicokinetics revealed high variability in Cmax and AUC. The indicated SD values are high for Cmax. In general, females had higher Cmax and exposure (AUC) than males. The AUC and Cmax values differed markedly between the three preparations tested without a consistent trend. E.g., the Mylan product had a lower AUC and Cmax than the two Lantus preparations in males whereas in females US-Lantus had the lowest AUC and Cmax.

Study G4668: 90-Day Repeat-Dose Toxicity of MYL-1501D and Lantus-IN in Wistar Rats

Toxicity and Pharmacodynamic Effect: The only adverse effects observed were 2 mortalities and clinical signs at the 0.38 mg/kg/day (high) dose; both deaths were related to the exaggerated pharmacodynamic effect of insulin glargine. Similar degrees and durations of glucose reduction were observed for all 3 test articles. The pharmacodynamic effects were consistent with the findings reported for Lantus.

Injection Site Effects: The injection site effects observed were generally independent of the dose and were considered to be related to the formulation or procedure, rather than insulin glargine itself. Local effects at the injection site have been reported for Lantus (EPAR 2012). Hence, the lower concentrations most likely did not have any significant impact on the conclusions of the study.

Immunogenicity: Low and comparable levels of binding antibodies were observed for the 3 test articles, independent of dose. Hence, the lower concentrations are not likely to have affected the results.

Toxicokinetics: The pharmacokinetic profile of MYL-1501D was found to be comparable with Lantus-EU, and for generally comparable with Lantus-US.

Study G4669: 90-day Repeat-dose Toxicity of MYL-1501D in New Zealand White Rabbits

Toxicity: There were no toxicological observations of concern. A single mortality (female) occurred during the course of treatment that was attributed to hypoglycaemia (i.e., exaggerated pharmacology of the test article). There were no adverse findings in either gender in any treatment group with respect to body weight, food consumption, haematology, clinical chemistry, organ weights, or gross and histopathological findings. Histopathological examination of injection sites at the end of the study identified slight local irritation in both the vehicle control and high dose groups. Animals dosed with vehicle control developed epidermal hyperplasia, parakeratosis, and inflammatory foci at the injection site. One female in the high-dose group developed minimal leukocyte infiltration at the injection site. In general, all findings were considered incidental and not related to the treatment.

Toxicokinetics: A dose-related increase in exposure to total insulin was observed on Days 1 and 90. No consistent gender difference was observed. MYL-1501D did not accumulate after repeated administration for 90 consecutive days.

In the *immunogenicity* analysis, no samples were positive for antidrug antibodies, indicating that MYL-1501D did not induce antidrug antibodies in rabbits.

Study U16176: 28d (+14d recovery) study in Wistar rats to compare Glargine Mylan from two different manufacturing processes; US-Lantus was another comparator.

There were no overt signs of toxicity in the study beyond the expected effects related to insulin pharmacology. Test agents MYL-1501D processes, and Lantus-US displayed similar directionality, magnitude, and duration of pharmacologic blood glucose reduction.

2.3.4. Ecotoxicity/environmental risk assessment

Insulin glargine is a recombinant human basal insulin analogue for the treatment of Type 1 (T1DM) and Type 2 diabetes (T2DM) mellitus.

According to the guideline EMEA/CHMP/SWP/4447/00 corr 1, proteins are exempted from the environmental risk assessment because they are unlikely to result in significant risk to the environment.

2.3.5. Discussion on non-clinical aspects

The applicant's pharmacology programme was generally in line with the CHMP insulin biosimilar guideline. Binding to and activation of (i.e. autophoshorylation) the two insulin receptor (IR) isoforms, IR-A and IR-B, were tested as well as three different metabolic effects (glucose uptake, adipogenesis and inhibition of lipolysis). Binding and activation tests were also done with the IGF-1 receptor (IGF1R) together with mitogenic action in cell culture. The results of these functional assays provided support for the claim of biosimilarity.

The functional assay of receptor activation, i.e. glucose uptake, was performed in an unusual way. The glucose uptake assay is a rather standardised procedure which measures the intracellular accumulation of radiolabelled 2-deoxy-glucose. However, the applicant measured consumption of glucose from the cell culture medium. Although this is less favourable since glucose consumption can depend on many different factors other than direct insulin-induced glucose entrance into the cell, the applicant has provided additional justifications during the application review that support the validity of the alternate glucose uptake assay format. The results from this assay showed similar glucose consumption. The applicant has later during the procedure provided two additional metabolic assays (adipogenesis and inhibition of lipolysis in 3T3-L1 cells) which are considered appropriate. Hence, the package of metabolic assays is acceptable.

The Glargine Mylan and the Lantus batches were not compared directly head-to-head in the various assays. Instead, each batch was tested separately against a working standard. This was done because the number of samples that can be processed per assay setup is limited and because the applicant intended to achieve comparability of the results across different experiments. The latter is not required for the non-clinical biosimilarity exercise. Rather, a direct head-to-head comparison of test and reference product within one experiment is suggested by the European biosimilarity guideline. By normalising the data to an internal standard as done by the applicant, information was lost because many data points were combined to yield a single relative potency value. However, the applicant submitted all raw data, and from these it can be concluded that the behaviour of glargine Mylan and Lantus was indeed similar in all assays performed.

The applicant also submitted in-vivo PD studies. These revealed the expected insulin effect (blood glucose lowering), however with a high inter-individual variability. For this reason, in-vivo studies are not required because they are considered too insensitive for detecting differences between the biosimilar and the reference product.

According to the current version of the European biosmilar guideline, toxicology studies are not necessary for a biosimilar application unless there is cause for concern. In the case of Mylan's insulin glargine, it

should be noted that it is produced in Pichia yeast, whereas the reference product is produced in E. coli, leading to low levels of glycosylated species in the test product vs. no glycosylated species in the reference product. However, the applicant achieved a reduction of the glycosylated forms to very low levels so that the potential toxicological impact of the glycosylated forms in Mylan's glargine is considered negligible. The most relevant repeat-dose study in rats (G11066), comparing a recent Mylan formulation with EU- and US-Lantus, revealed no toxicological concerns.

2.3.6. Conclusion on non-clinical aspects

The non-clinical programme for Semglee is in line with CHMP guidelines and, regarding in vivo studies, exceeds the requirements. The results provided support a claim of biosimilarity.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical phase I and phase III trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Studies	Category	Comparator	Purpose of Study
GLARGCT100111: PK/PD clamp study in T1DM (Germany)	Pivotal	Lantus-EU and Lantus-US	To compare PK and PD parameters and safety between MYL-1501D, Lantus-EU and Lantus US.
MYL-GAI-3001: safety, efficacy, and immunogenicity study in T1DM (Global)	Pivotal	Lantus-US	To compare efficacy, immunogenicity, and safety of MYL-1501D with that of Lantus-US
FFP-112-01: PK/PD clamp study in NHV (Japan)	Supportive	Lantus-JP	To compare the PK/PD characteristics and safety of MYL-1501D and Lantus-JP
FFP-112-02: safety, efficacy, and immunogenicity in T1DM (Japan)	Supportive	Lantus-JP	To compare efficacy, immunogenicity, and safety of MYL-1501D with that of Lantus-JP

CLG031/BIO012/DM/GLA/2007: Safety, efficacy, and immunogenicity in T1DM (India)	Supportive	Lantus-IN	To compare the safety and efficacy of MYL-1501D with Lantus-IN

2.4.2. Pharmacokinetics

The Semglee clinical pharmacology programme consisted of two studies, which were single dose crossover euglycaemic clamp studies. In respect to this application study GLARGCT100111 was conducted to demonstrate definitive PD and PK similarity between Semglee and Lantus EU in T1DM subjects.

GLARGCT100111 was a single-center, randomized, double-blind, single-dose, 3-way crossover euglycemic clamp, active controlled study.

The size of the batch used in this study is considered sufficiently large. The intended commercial batch size is 900 kg.

Primary objectives: To compare the relative pharmacokinetic and pharmacodynamics properties of Semglee with Lantus (EU and US) in subjects with type 1 diabetes mellitus.

Secondary objectives: To assess the single dose safety and local tolerability of Semglee relative to Lantus (EU and US).

The primary PK endpoints were area under the plasma insulin concentration curve from 0 to 30 hours ($AUC_{ins.0-30h}$) and maximum insulin concentration ($C_{ins.max}$). The secondary PK parameters were $AUC_{ins.0-6h}$, $AUC_{ins.6-30h}$, $AUC_{ins.0-\infty}$, t_{max}, $t_{½}$ and terminal elimination rate constant (λ_z).

According to study protocol it was planned to determine insulin glargine concentrations and related pharmacokinetic parameters from ELISA.

Pharmacokinetic data analysis

Quantification of the insulin glargine concentration with the ELISA gave implausible results. Furthermore, GLP deficiencies in the analytical laboratory were identified. To address the technical difficulties of evaluating insulin glargine data with an assay that has different cross-reactivity for insulin glargine and human insulin and in response to a recommendation from the FDA, a specific LC MS/MS method to measure insulin glargine and its metabolites insulin glargine M1 and insulin glargine M2 in backup patient samples from the study was developed. This analysis is considered pivotal.

Statistical methods

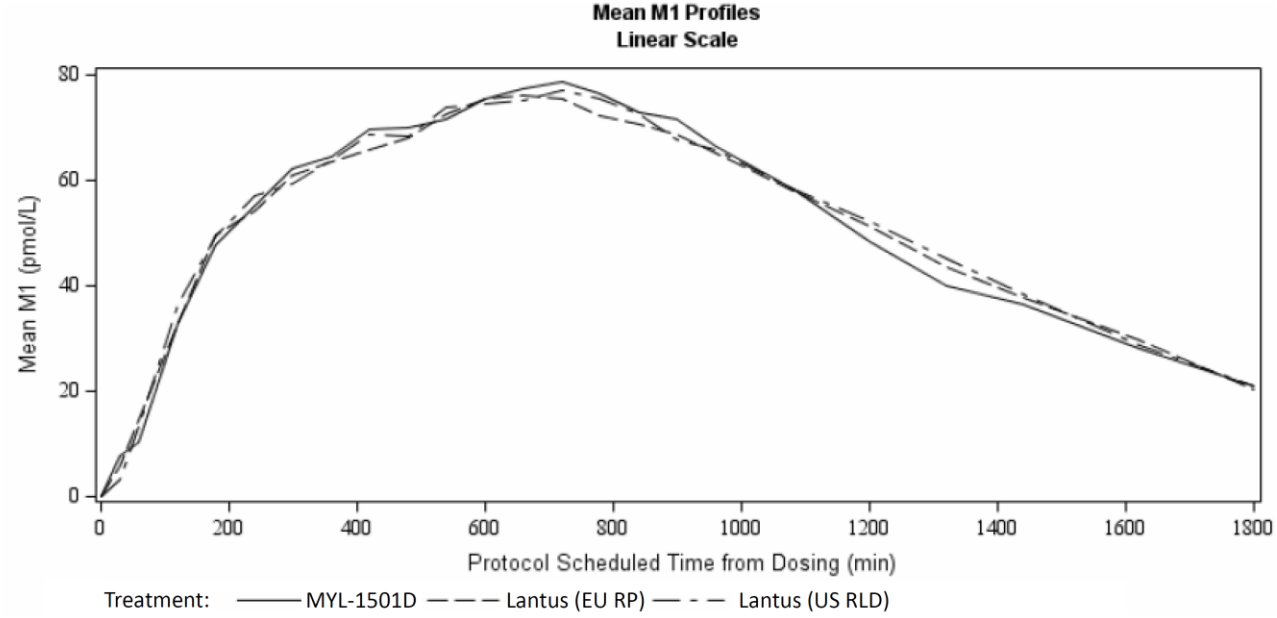
Analysis of PK data is based on the PK-Full-Analysis-Set. Log-transformed primary endpoints, $AUC_{ins.0-30h}$ and $C_{ins.max}$, for all treatments (Semglee, Lantus EU and Lantus US) are analysed using a linear mixed effect model with treatment and period as fixed and subject as a random factor. The estimated geometric mean ratios and their 90% confidence intervals (CI) are calculated by exponentially transforming corresponding treatment contrasts (log scale) and CIs obtained from the mixed model. If the exponentially transformed 90% CIs for $AUC_{ins.0-30h}$ and $C_{ins.max}$ fell within the limits 0.8-1.25, bioequivalence was accepted. Secondary AUC-based PK endpoints are analysed using the same approach, but CIs are not required to fulfil the 0.8-1.25 limits.

Results

A total of 114 subjects were included in the study, 2 subjects withdrew consent after the first treatment (Lantus EU), 1 subject was excluded from analyses because he was included into the study although fulfilling an exclusion criterion.

LC MS/MS

As seen during the blinded data review, median insulin glargine and M2 concentrations were below LLoQ at each time point. Thus, the following evaluations focus on the pharmacokinetic evaluations of M1, the predominant insulin glargine metabolite.



Summary Statistics of Pharmacokinetic Endpoints (unadjusted); PK Analysis Set; Metabolite M1

Parameter	Treatment	N	Geo Mean	CV%	Median	Min-Max
Primary PK endpoints						
$AUC_{ins.0-30h}$ [pmol*h/L]	Lantus EU	86	1336	63.68	1335	480.3 – 6003
	Lantus US	87	1362	66.61	1294	525.5 - 7994
	Semglee	87	1360	63.35	1262	554.4 – 6883
$C_{ins.max}$ [pmol/L]	Lantus EU	86	80.63	49.09	73.82	39.47 – 288.7
	Lantus US	87	79.82	62.78	75.30	42.60 - 483.4
	Semglee	87	83.63	51.96	77.73	45.91 – 361.7
Secondary PK endpoints: AUC						
$AUC_{ins.0-\infty}$ [pmol*h/L]	Lantus EU	46	2243	41.47	5215	1495 – 18719
	Semglee	51	2241	65.15	4402	1349 – 17807
$AUC_{ins.0-6h}$ [pmol*h/L]	Lantus EU	86	NC	64.86	739.3	90.35 – 3829
	Semglee	87	NC	63.18	663.3	90.35 – 3598
$AUC_{ins.6-30h}$ [pmol*h/L]	Lantus EU	86	1111	66.55	2500	361.4 – 14214
	Semglee	87	1138	66.47	2448	361.4 – 15614
Secondary PK endpoints: Time parameters						
			Mean	**SD**		
t_{max} [h]	Lantus EU	86	11.57	3.6	12	3 – 22
	Semglee	87	11.21	3.621	12	0.5 - 20
λ_z [/h]	Lantus EU	46	0.0606	0.0332	0.0589	0.0107 – 0.217
	Semglee	51	0.0690	0.0431	0.0531	0.0214 – 0.228
$t_{½}$ [h]	Lantus EU	46	14.75	9.620	11.76	3.190 – 64.64
	Semglee	51	13.24	6.621	13.06	3.044 – 32.36

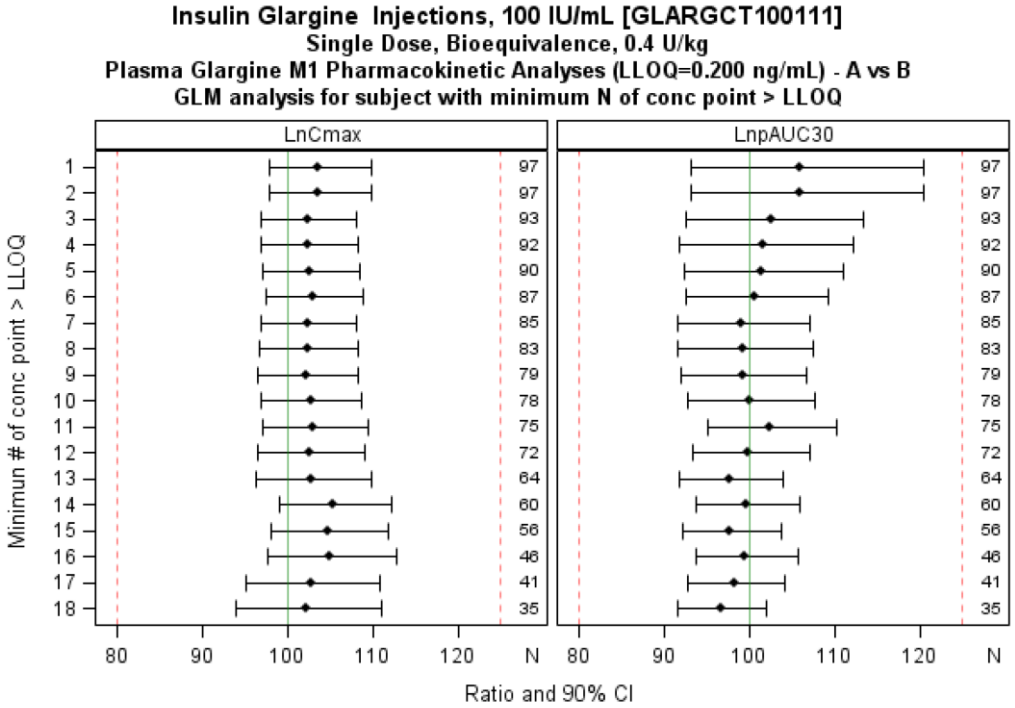
Parametric Analysis of the Primary Pharmacokinetic Endpoints; (PK Analysis Set; Metabolite M1)

Parameter	Product(s)	N	Geo Mean*	90% CI
$AUC_{ins.0-30h}$ [pmol*h/L]	Lantus EU	86	1310	1209; 1419
	Lantus US	87	1301	1201; 1409
	Semglee	87	1328	1226; 1438
	Semglee vs. Lantus EU	72	1.01	0.95; 1.09
	Semglee vs. Lantus US	74	1.02	0.95; 1.09
	Lantus EU vs. Lantus US	72	1.01	0.94; 1.08
$C_{ins.max}$ [pmol/L]	Lantus EU	86	79.3	76.7; 87.4
	Lantus US	87	77.9	72.9; 83.1
	Semglee	87	81.9	178; 213
	Semglee vs. Lantus EU	72	1.03	0.97; 1.10
	Semglee vs. Lantus US	74	1.05	0.99; 1.12
	Lantus EU vs. Lantus US	72	1.02	0.96; 1.08

* the geometric means shown in this analysis table are based on least-square means within the ANOVA and are adjusted for other effects in the model

M1 determination with LC-MS/MS was quite insensitive (LLoQ = 0.2 ng/mL). This rather high LLoQ led to exclusion of many profiles, and only 72 out of 111 subjects treated with Semglee and Lantus EU could be included in the primary analysis. However, sensitivity analyses provided by the applicant range from including all subjects to including only subjects with profiles that have specific minimum numbers of evaluable measurements.

Sensitivity analysis for MIG vs EU Reference, based on M1 concentrations observed above the LLoQ of 0.2 ng/mL

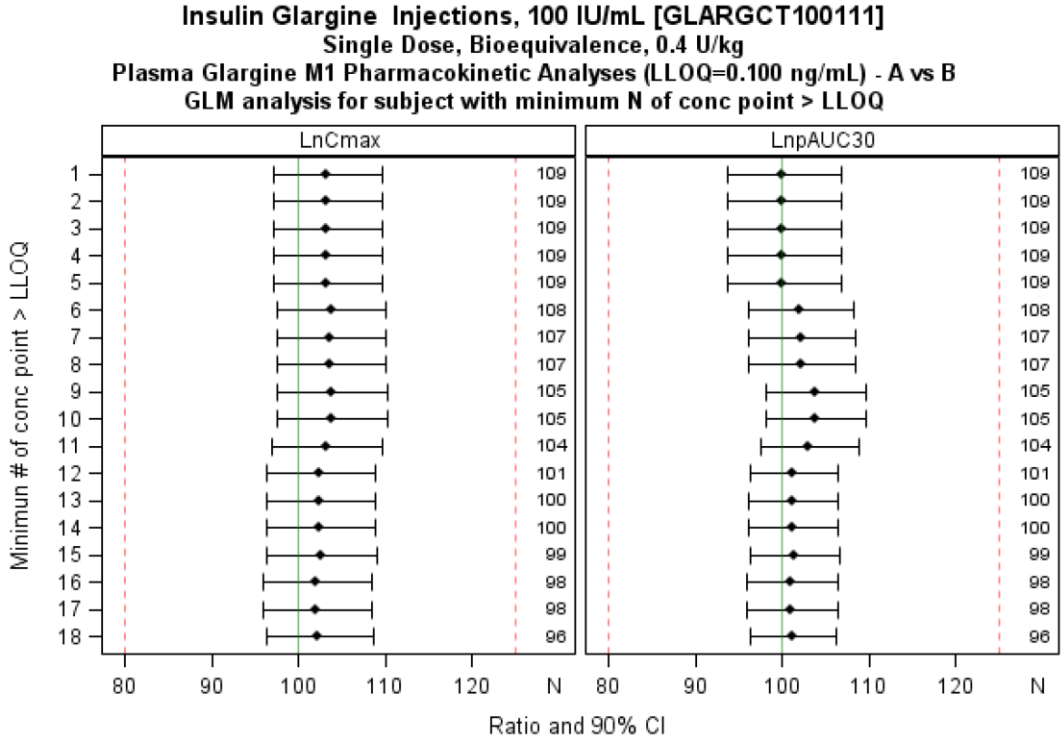


Treatment A: Insulin glargine (MYL-1501D), 100 IU/mL in 10.0 mL vials
Treatment B: Insulin glargine (Lantus), 100 IU/mL in 3.0 ml cartidges (EU RP)

The number of subjects with paired data meeting this requirement is provided along the right side of each parameter listing.

A further sensitivity analysis was also provided based on M1 concentration with an extrapolated LLoQ of 0.1 ng/ml, leading to an increased number of M1 concentration measurements included in the analyses, see figure below.

Sensitivity analysis for MIG vs EU Reference, based on M1 concentrations with extrapolated LLoQ above 0.1 ng/mL including patients with predose concentrations greater than 5% of Cmax



Treatment A: Insulin glargine (MYL-1501D), 100 IU/mL in 10.0 mL vials
Treatment B: Insulin glargine (Lantus), 100 IU/mL in 3.0 ml cartidges (EU RP)

The number of subjects with paired data meeting this requirement is provided along the right side of each parameter listing.

All these sensitivity analyses yield similar conclusions, and equivalence criteria are met for all analyses.

2.4.3. Pharmacodynamics

PD was evaluated as part of the PK study using an automated hyperinsulinemic euglycemic clamp method. Study duration after administration of test or reference was 30 hours. Subjects were connected to a Biostator at 1-6 hours prior to administration of trial drug. The subjects remained fasting during the entire glucose clamp. A variable infusion of human regular soluble insulin or glucose was initiated in order to obtain a blood glucose level of 5.5 mmol/L (100 mg/dL). This level (±20%) had to be kept continuously for at least 1 hour before trial product administration. At 20 minutes prior to trial product administration the insulin infusion was completely terminated. The body weight at Visit 2 was used to calculate the dose for all three clamp experiments at Visit 2, 3 and 4.

After trial drug administration, a variable i.v. infusion of a 20% glucose solution was initiated by the Biostator, which automatically calculated the appropriate glucose infusion rate (GIR) to keep the glucose

concentration constant at the glucose clamp target of 5.5 mmol/L. In case a high glucose infusion rate (GIR) was necessary, a part of the glucose infusion was done by an external pump.

The blood glucose measurements of the Biostator were re-calibrated at regular intervals (at least every 30 minutes) by blood glucose measurements performed with a laboratory method (Super GL Glucose Analyzer).

Statistical methods

The analysis of PD data was based on the PD-Full-Analysis-Set. Log-transformed primary PD endpoints $AUC_{GIR.0\text{-}30h}$ and GIR_{max} were analysed in the same way as primary PK endpoints. However, besides 90% CIs also 95% CIs were provided for geometric mean ratios. Secondary PD endpoints $AUC_{GIR.0\text{-}6h}$ and $AUC_{GIR.6\text{-}30h}$ were analysed using the same statistical approach as applied for the primary endpoints, but CIs for these endpoints are not required to fulfil specific requirements.

GIR_{max} and $tGIR_{max}$ were derived from smoothed GIR profiles. Smoothing was done using a locally weighted regression technique (SAS procedure PROC LOESS) with smoothing parameter 0.3.

Results

In general, the analysis of pharmacodynamic data was done as outlined in the protocol / statistical analysis plan. Inspection of the blinded to sequence (but not blinded to subject ID) PD data, however, revealed a number of profiles which had no glucose infusion requirements during a clamp period. In these cases, $AUC_{GIR.0\text{-}30h}$ and GIR_{max} are equal to zero and no log-transformation is possible. In addition, several subjects had very low glucose infusion requirements. Therefore, it was decided in the first Database Release Meeting that all subjects with any profiles of $AUC_{GIR.0\text{-}30h} \leq 50$ (h*mg/kg/min) should be excluded from the primary PD analysis.

Four, six and five subjects were excluded for Semglee, Lantus EU and Lantus US, respectively.

In addition, it was decided at the Database Release Meeting that four subjects (Lantus US: 1; Lantus EU: 2; Semglee: 1) were to be excluded from GIR_{max} analysis due to technical problems which lead to obviously incorrect GIR_{max} values.

Summary of the Pharmacodynamic Endpoints

(114 subjects were included in the study, 2 subjects withdrew consent after the first treatment (Lantus EU), 1 subject was excluded from the efficacy analysis because he was included into the study although fulfilling an exclusion criterion)

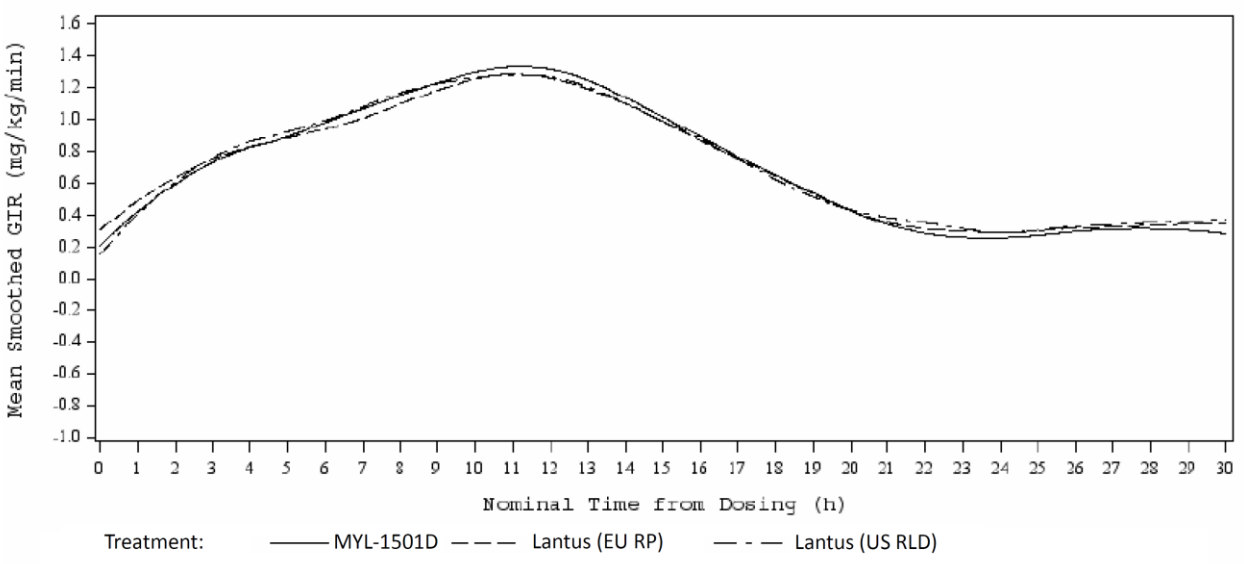
Pharmacodynamic Endpoints (unadjusted); PD Analysis Set; excluding profiles with $AUC_{GIR0\text{-}30} \leqslant 50$ (h*mg/kg/min)

Parameter	Treatment	N	Geo Mean	CV%	Median	Min-Max
Primary PD endpoints						
$AUC_{GIR0\text{-}30h}$ [mg/kg]	Lantus EU	107	1015	69.1	1145	96; 4310
	Lantus US	106	1047	62.7	1218	53 - 4452
	Semglee	107	961.8	70.6	1149	53.35; 4675
GIR_{max} [mg/kg/min]	Lantus EU	106	1.38	55.1	1.43	0.31; 4.82
	Lantus US	105	1.41	60.4	1.48	0.23; 8.27
	Semglee	106	1.39	61.1	1.5	0.21; 5.38
Secondary PD endpoints:						
$AUC_{GIR.0\text{-}6h}$ (mg/kg)	Lantus EU	113	253	91.4	213.9	0; 1045
	Semglee	111	245	85.4	232.4	0; 818.4
$AUC_{GIR.6\text{-}30h}$ (mg/kg)	Lantus EU	113	1022	74.5	852.6	0; 3625

	Semglee	111	1037	74.7	920.7	0; 3856
$tGIR_{max}$ (h)	Lantus EU	111	11.3*	5.98**	11	0; 30
	Semglee	110	11.1*	6.36**	10.8	0; 30

* mean; ** SD

Mean smoothed Glucose injection rate (GIR) over time



Parametric Analysis of the Primary Pharmacodynamic Endpoints; (PD Analysis Set; excluding profiles with $AUC_{GIR0-30}$ ⩽50 (h*mg/kg/min))

Parameter	Product(s)	N	Geo Mean*	95% CI
$AUC_{GIR0-30h}$ [mg/kg]	Lantus EU	107	988	837; 1166
	Lantus US	106	1022	866; 1206
	Semglee	107	956	811; 1128
	Semglee vs. Lantus EU	104	0.97	0.82; 1.14
	Semglee vs. Lantus US	103	0.94	0.80; 1.10
	Lantus EU vs. Lantus US	104	0.97	0.82; 1.14
GIR_{max} [mg/kg/min]	Lantus EU	106	1.38	1.23; 1.53
	Lantus US	105	1.40	1.25; 1.56
	Semglee	106	1.38	1.24; 1.54
	Semglee vs. Lantus EU	103	1.01	0.91; 1.11
	Semglee vs. Lantus US	102	0.99	0.89; 1.10
	Lantus EU vs. Lantus US	102	0.98	0.89; 1.09

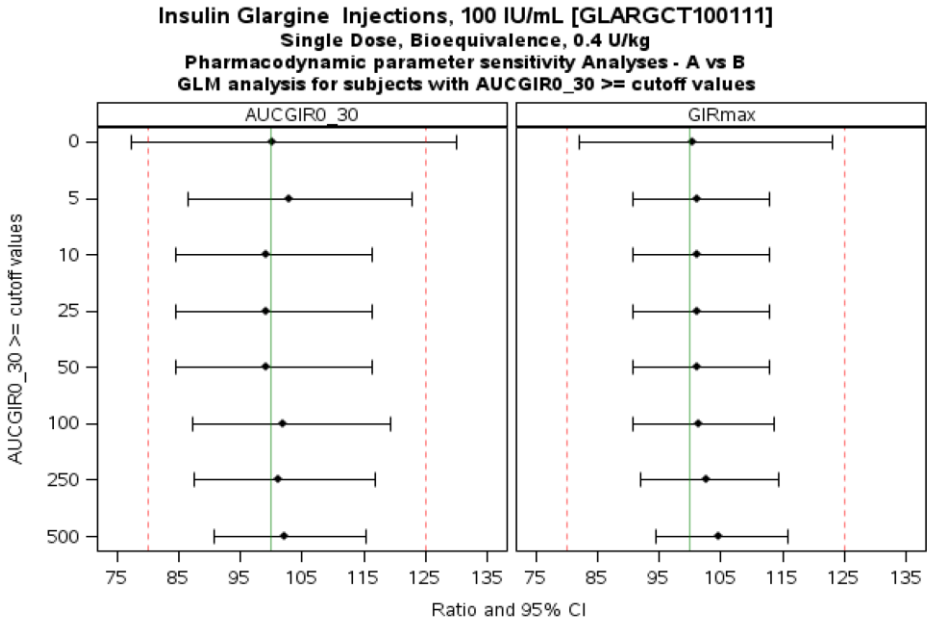
* the geometric means shown in this analysis table are based on least-square means within the ANOVA and are adjusted for other effects in the model

Anlaysis of the Primary Pharmacodynamic Endpoints (subjects with $AUCGIR_{0-30h}$ ⩽50 h*mg/kg/min included)

Parameter	Product(s)	N*	Geo Mean	95% CI
$AUC_{GIR0-30h}$ [mg/kg]	Lantus EU	113	741	557.3; 985.1
	Semglee	111	759	569; 1011
	Semglee vs. Lantus EU	111	1.02	0.782; 1.34
GIR_{max} [mg/kg/min]	Lantus EU	111	1.08	0.87;1.34
	Semglee	110	1.13	0.91;1.40
	Semglee vs. Lantus EU	108	1.04	0.85;1.28

In the primary analysis for Study GLARGCT100111, a cutoff value based on $AUCGIR_{0\text{-}30h}$ of 50 mg/kg/min, which was approximately 5% of the mean $AUCGIR_{0\text{-}30h}$, was used. A PD sensitivity analysis was conducted for which geometric mean and 95% CI were calculated when using different cut-off values, ranging from 5 h*mg/kg/min to 500 h*mg/kg/min (around 0.5% to 50% of the mean $AUCGIR_{0\text{-}30h}$). The outcome of this analysis in respect to $AUCGIR_{0\text{-}30h}$ and GIR_{max} is graphically shown in the figure below. For all tested cut-offs greater than zero the 95% CI lies within the desired range. The mean ratios are always close to unity.

Sensitivity analysis for geometric mean ratio, based on PD data



Treatment A: Insulin glargine (MYL-1501D), 100 IU/mL in 10.0 mL vials
Treatment B: Insulin glargine (Lantus), 100 IU/mL in 3.0 ml cartidges (EU RP)

For Geometric Mean analysis, in cases of zero, the parameters $AUCGIR_{0\text{-}30h}$ and GIR_{max} were set to the lowest value greater than 0 (over all subjects), which were 0.94 for $AUCGIR_{0\text{-}30h}$ and 0.0044067 for GIR_{max}.

Zero values do not allow calculation of a geometric mean; therefore, in case of AUCGIR = 0 and GIR_{max} = 0, a small non-zero value must be assumed to allow calculation of the geometric mean. In consequence, the resulting geometric mean depends on the value selected for substituting zero. Thus, in case of the cut-off point zero, the ratios and CIs are somewhat arbitrary. The method for selecting a suitable substitution for zero AUCGIR values is explained in the footnote of the table and is considered appropriate. Even with the lowest non-zero cut-off value (5 h*mg/kg/min, 0.5% of mean $AUCGIR_{0\text{-}30h}$) the desired 95% CI is clearly met. Therefore, this sensitivity analysis implies that disregarded subjects with low AUCGIR did not introduce bias.

2.4.4. Discussion on clinical pharmacology

The design of the PK/PD study was generally in line with the biosimilar insulin guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1). The automated hyperinsulinemic euglycaemic clamp used in the study is regarded as the most accurate method for comparing the PD effect of insulins and insulin

analogues. The duration of the clamp was 30 hours, which is greater than the minimum length of 24 hours recommended by the guideline.

The pharmacokinetic evaluation was restricted to M1, the predominant insulin glargine metabolite, which is acceptable since the parent drug is immediately converted and therefore not measurable. M1 determination with LC-MS/MS was quite insensitive (LLoQ = 0.2 ng/mL) which, however, was the usual sensitivity of this new glargine-specific assay at that time. This rather high LLoQ led to exclusion of about one third of subjects from the primary PK analysis. However, several sensitivity analyses were provided by the applicant, ranging from including all subjects to including only subjects with profiles that had a certain minimum of evaluable measurements and sensitivity analyses using different LLoQs. All these sensitivity analyses yield similar conclusions and equivalence criteria are well met for all analyses. There is no indication for introduction of a relevant bias by the exclusion of several PK-profiles due to the LLoQ for M1 of 0.2 ng/mL. The PK results can be considered robust. Therefore, the PK results support a conclusion of biosimilarity.

The primary analysis of PD endpoints as presented by the applicant deviates from the study protocol/statistical analysis plan as, although a "blinded" review of the data was foreseen, no specific cut-off value for exclusion of low GIR-profiles was pre-specified. Based on this "blinded" review of data, the applicant decided to exclude subjects with any profile of $AUC_{GIR.0-30h} \leq 50$ (mg/kg). This analysis yielded 95% CIs meeting the pre-defined acceptance range of 80-125%. However, including all profiles and using the pre-specified analysis of log-transformed data, the 95% confidence intervals for the Semglee versus Lantus EU comparison were not contained within the pre-specified margins for either primary PD endpoint ($AUCGIR_{0-30}$: 1.02 [0.782;1.34] and GIR_{max}: 1.04 [0.85;1,28]).

The latter analysis should still be considered primary since the cut-off value for exclusion of low profiles was not prespecified and exclusion of low profiles increases the chance to conclude equivalence. In addition, reviewers were blinded to sequence but not blinded to subject ID. Hence, equivalence with regard to PD endpoints was formally not shown.

However, 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) does not mandatorily require the PD results as primary endpoint. The guideline states with respect to PD endpoints: *If, based on comprehensive analytical characterisation and non-clinical in vitro tests using sensitive, orthogonal and state-of-the art methods, close similarity in physicochemical and functional characteristics can clearly be shown for the biosimilar and the reference insulin, all GIR-related parameters may be defined as secondary endpoints. Nevertheless, the PD results should always reasonably support the PK results.*

The data presented by the applicant in respect to analytical characterisation and non-clinical in vitro tests indicate similarity between MYL-1501D and EU-insulin glargine and results of the functional assays are reliable. Thus, similarity at the analytical and functional level together with PK similarity makes it unlikely that the variability in the PD data reflects product-related dissimilarity. Hence, GIR endpoints can be considered as secondary endpoints. Based on analytical and non-clinical data GIR endpoints can be considered as secondary endpoints. There is no evidence that the PD analysis with the 95% confidence intervals for the MYL-1501D versus Lantus-EU comparison being outside the pre-specified 80% to 125% margins for both $AUCGIR_{0-30h}$ and GIR_{max} is due to true differences in PD behaviour.

The Applicant argued that low insulin response is neither specific to this study nor related to insulin resistance, that it was equally distributed between treatments and that low responses were not always seen in the same subjects, but rather occurred inconsistently (usually in just 1 out of 3 clamps).

Furthermore, the mean ratio remained close to 1 in all presented analyses supporting the notion that intra-individual variability is the likely cause for not meeting the primary objective.

Since low responses complicate an analysis based on log-transformed data and increases the variance, the applicant provided results of an analysis based on the non-transformed data (i.e. assuming normality) including profiles of all subjects. This additional analysis resulted in CIs that are well within the 80-125% margins (AUCGIR: 0.997 [0.887;1.122] and GIR_{max}: 1.04 [0.941;1.153]). Neither log-transformed nor non-transformed data histograms of studentized residuals seem to indicate relevant deviations from the distributional assumption.

Furthermore, the applicant provided additional sensitivity analyses for PD data that used different cut-offs for data exclusion (ranging from no exclusion to exclusion of profiles with AUCGIR≤500 mg/kg/min) to understand robustness of data and to evaluate any bias. All these analyses showed similar point estimates close to 1 with CIs getting tighter when excluding low profiles.

In summary, there is no indicator that the PD analysis with the 95% confidence intervals for the MYL-1501D versus Lantus-EU comparison being outside the pre-specified 80% to 125% margins for both $AUCGIR_{0-30h}$ and GIR_{max} is due to true differences in PD-kinetics. The PD results can best be explained by intraindividual variability of study subjects. PD data reasonably support PK results.

2.4.5. Conclusions on clinical pharmacology

A time interval of 0-30 hours post-dose is acceptable for a long acting insulin.

Due to the difficulties with the ELISA-assay, the additional LC MS/MS quantification of the insulin glargine metabolite M1 is considered the pivotal assay. This analysis is burdened by a low sensitivity resulting in a high number of concentration profiles which had been excluded from analysis. However, supported by sensitivity analyses all fulfilling equivalence criteria, similarity between the pharmacokinetics of Semglee and Lantus EU can be concluded.

Deviating from the protocol and SAP, profiles with $AUC_{GIR.0-30h} \leq 50$ (mg/kg) were excluded from the analysis of PD endpoints based on data not blinded to subject ID. This is in general not acceptable.

Primary focus should therefore be on the pre-specified analysis including all patients. This analysis failed to show equivalence since the corresponding 95% confidence intervals were not contained within the pre-specified margins ($AUCGIR_{0-30}$: 1.02 [0.782;1.34] and GIR_{max}: 1.04 [0.85;1,28]).

However, the data presented by the applicant in respect to analytical characterisation and non-clinical in vitro tests indicate similarity between MYL-1501D and EU-insulin glargine and results of the functional assays are reliable. Thus, similarity at the analytical and functional level together with PK similarity makes it unlikely that the variability in the PD data reflects product-related dissimilarity. Hence, GIR endpoints can be considered as secondary endpoints in line with the "Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues" (EMEA/CHMP/BMWP/32775/2005_Rev. 1).

While equivalence for PD endpoints is not formally shown, PD results still reasonably support PK data. For PD endpoints, the mean ratio remained close to 1 independent of number of subjects excluded with confidence intervals becoming tighter when excluding low profiles. Low GIR responses were not always seen in the same subjects, but rather occurred inconsistently (usually in just 1 out of 3 clamps) and were equally distributed between treatments. An analysis based on non-transformed data including all subjects/profiles might have been an alternative option and results in confidence intervals that are well within the 80-125% margin (AUCGIR: 0.997 [0.887;1.122] and GIR_{max}: 1.04 [0.941;1.153]).

In summary, there is no indicator that the PD analysis with the 95% confidence intervals for the MYL-1501D versus Lantus-EU comparison being outside the pre-specified 80% to 125% margins for both $AUCGIR_{0\text{-}30h}$ and GIR_{max} is due to true differences in PD behaviour. The PD results can best be explained by intraindividual variability of study subjects. PD data reasonably support PK results.

2.5. Clinical efficacy

Introduction

MYL-1501D (also described as MYL-1501D, Glargine Mylan) has been developed to be a biosimilar product to Lantus. The Company is seeking approval for the same indication as the one approved for Lantus, i.e. for the treatment of diabetes mellitus in adults and children over 2 years of age.

Dose response study

- N/A

Main studies

One phase III study was conducted with MYL-1501D to compare efficacy, safety and immunogenicity of MYL501D with Lantus US in patients with T1DM. Results are presented at week 24, the study has been ongoing at time of submission. The study was conducted with formulation D, the formulation intended for commercialization in the EU. The key goal of this study was to demonstrate a similar glycaemic efficacy with similar insulin doses between MYL501D and Lantus and to demonstrate safety, with a focus on immunogenicity, between the MYL501D and Lantus treatment groups.

In addition, Clinical study reports (CSRs) of 2 supporting safety/efficacy studies conducted by Mylan's co-development partner Biocon with another partner for Japan were submitted.

Study MYL-GAI-3002 (safety/ efficacy/ immunogenicity study in **T2DM**) and Study MYL-1501D-3003 (to study the interchangeability of MYL-1501D with Lantus) are ongoing; no efficacy results are submitted yet.

As these studies are not formal requirements according to the Guideline on similar medicinal products containing recombinant human insulin they are only considered as supportive for efficacy. The euglycemic PK/PD clamp studies are considered pivotal to demonstrate comparable efficacy. In this overview detailed information is given for study MYL-GAI-3001 (details on supportive studies are given in the Clinical AR):

Study MYL-GAI-3001: open-label, randomized, multi-center, parallel-group study to compare the efficacy and safety of MYL-1501D with Lantus-US in T1DM patients. Results at week 24 were presented within the initial submission (protocol number: MYL-GAI-3001); 52 week results were submitted with the responses to the Day 120 List of Questions. The primary endpoint of the study was change in HbA1c at Week 24; in the following, 24 week results and 52 week results are provided. An overview is given in the following table:

Summary of efficacy for trial MYL-GAI-3001

Title: An Open-label, Randomized, Multi-center, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus in Type 1 Diabetes Mellitus Patients.			
Study identifier	MYL-GAI-3001		
Design	open-label, randomized, parallel-group		
	Screening Duration of Run-in phase: Duration of main phase: follow-up		up to 4 weeks 6 weeks 52 weeks 4 weeks
Hypothesis	non-inferiority		
Treatments groups	MYL IG		glargine Mylan, N=280
	EU-Lantus		Lantus, N=278
Endpoints and definitions	Primary endpoint	HbA1c	change in HbA1c from baseline to week 24
	Secondary endpoints	HbA1c	change from baseline by visit
		FPG	change from baseline in fasting plasma glucose at week 24 and by visit
		8-point SMBG profile	change from baseline
		daily basal insulin dose	change from baseline
		daily mealtime insulin dose	change from baseline
		total daily insulin dose	change from baseline
		proportion of patients with HbA1c <7%	proportion of patients in each group meeting the therapeutic target (HbA1c <7%) at Week 24.
		proportion of patients meeting rescue criteria	proportion of patients meeting an HbA1c increase of >1% over baseline at week 12 compared to baseline
Database lock	ongoing, SAE cutoff date: June 1, 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat week 24		
Descriptive statistics and estimate variability	Treatment group	glargine Mylan	Lantus
	Number of subject	see at actual endpoint	see at actual endpoint
	change from baseline in HbA1c at week 24, LS mean (SE) (%)	N=280 0.14 (0.054)	N=277 0.11 (0.054)

	change from baseline in FPG at week 24, mean (SD) (mmol/L)	N=264 -0.81 (4.485)	N=264 0.09 (4.507)
	the 8-point SMBG profile, change from baseline at week 24	please see in the body of assessment	please see in the body of assessment
	daily basal insulin dose, change from baseline at week 24, mean (SD), (U/kg)	N=265 0.0152 (0.04528)	N=261 0.0039 (0.04098)
	total daily insulin dose, change from baseline at week 24, mean (SD), (U/kg)	N=265 0.0203 (0.09962)	N=261 0.0127 (0.10871)
	total mealtime insulin dose, change from baseline at week 24, mean (SD), (U/kg)	N= 265 0.3671 (0.16480)	N= 264 0.3596 (0.1568)
	Proportion of Patients with HbA1c <7% , number of responders (%)	N=280 responders: 73(26.1%) missing: 12	N=277 responders: 84 (30.3) missing: 13
	Proportion of Patients Meeting Rescue Criteria	please see in the body of assessment	please see in the body of assessment
Effect estimate per comparison	Primary endpoint: HbA1c, change from baseline at week 24	Comparison groups	glargine Mylan- Lantus
		LS Mean Difference (SE)	0.03 (0.046)
		95% CI for difference	-0.066, 0.117
	FPG, change from baseline at week 24	difference in means	-0.90
		95% CI of difference	-1.364, -0.133
		P-value	0.017
	daily basal insulin dose, change from	difference in means	0.0113
		95% CI of difference	0.004,0.019

	baseline at week 24	P-value	0.002
	total mealtime insulin dose, change from baseline at week 24	difference in means	-0.0075
		95% CI of difference	-0.021, 0.011
		P-value	0.574
	total daily insulin dose, change from baseline at week 24	difference in means	0.0076
		95% CI of difference	-0.011, 0.025
		P-value	0.441
	Proportion of Patients with HbA1c <7%	P-value	0.250
Notes	-		

Study centers: 164 study centers in North America (United States, Canada), European Union (EU) (Czech Republic, Estonia, Germany, Hungary, Latvia, Romania, Slovakia, United Kingdom [UK]), and South Africa.

Study period: 18 August 2014 (first patient enrolled) - 07 July 2016 (Last Patient Completed; Week 52).

Objectives (objectives pertaining to safety are marked in *bold,* for results on these objectives it is referred to the safety part of this AR):

Primary Objective: to test whether MYL- 1501D once daily was non-inferior to Lantus® once daily (based on change in HbA1c from baseline to 24 weeks) when administered in combination with mealtime insulin lispro.

Secondary Objectives:

-to compare MYL-1501D to Lantus®, at 24 weeks and 52 weeks, when administered in combination with mealtime insulin lispro with respect to the following:

1. Immunogenicity: change from baseline in titer, incidence of anti-drug antibodies (ADA), and anti-host cell protein (anti-HCP) antibodies

2. Rate per 30 days of hypoglycemic events

3. Occurrence of local reactions, systemic reactions, and other adverse events (AEs)

4. Device-related safety assessment

5. Change in HbA1c from baseline at other scheduled visits

6. Change in fasting plasma glucose (FPG) from baseline

7. Change in basal insulin dose per unit body weight (U/kg) from baseline

8. Change in 8-point self-monitor blood glucose (SMBG) profile from baseline

9. Proportion of participants with HbA1c <7% at 24 weeks.

Design and conduct: following a 4-week screening period, all patients were shifted from their current mealtime insulin to Humalog and were titrated on Lantus during a six-week run-in period. Thereafter, patients were randomised to either Lantus or MYL1501D; after all patients had been exposed to 24 weeks of treatment, data were unblinded and an analysis for the primary endpoint was performed. An overview of the study design is given in the following table:

Treatments

Test Product, dose and mode of administration, batch number: Mylan's insulin glargine 100 IU/mL provided in a pre-filled disposable pen with a 3 mL cartridge was administered as a subcutaneous injection dosed as prescribed by the treating physician for the patient's need. The batch numbers were as follows: D050010, D050011, D050012, D050016, D050015, and BF15002786.

Reference Therapy, dose and mode of administration, batch number: Lantus (100 IU/mL) provided in a pre-filled disposable pen with a 3 mL cartridge was administered as a subcutaneous injection dosed as prescribed by the treating physician for the patient's need. The batch numbers were as follows: 4F924A, 4F723A, 4F1034A, and 5F1346A.

Mealtime Insulin (non-investigational medicinal product), batch number:

Humalog (insulin lispro), referred to as mealtime insulin, provided in Kwikpen disposable pens (100 U/mL) and administered as subcutaneous injections as prescribed by the treating physician for the patients' need. The batch numbers were as follows: C179320A, C276579A, C355204A, C269495D, C318195, and C400644.

Patient population

It was planned to randomize 500 patients; 832 patients were screened and 558 patients were randomized. A total of 557 patients were analyzed for efficacy and 558 patients were analyzed for safety. Patients with established diagnosis of T1DM per American Diabetes Association 2014 criteria who fulfilled the following criteria were included in this study:

1. Initiation of insulin treatment within 6 months of T1DM diagnosis
2. Treatment with basal-bolus insulin therapy for at least 1 year before screening
3. Fasting plasma C-peptide <0.3 nmol/L at screening
4. Patient was treated with once-daily Lantus at stable dose (±15% variation in dose) for at least 3 months at screening
5. Glycosylated hemoglobin ≤9.5% at screening
6. Male or female, age between 18 to 65 years.

Blinding: the study was conducted open-label. To minimize bias, the treatment assignments were not revealed to the bioanalytical laboratory for the antibody determinations, the central laboratory for the safety (clinical safety laboratory and immunogenicity) and efficacy (HbA1c) analyses, and for study members who were not in direct contact with the centers during conduct of the study. The investigator and patients were not blinded to the treatment assignments. In addition, before the interim database lock, study team members who were involved in making analysis-related decisions such as excluding subjects for the PP population, were also blinded.

Statistical methods

The primary efficacy outcome was change in HbA1c from baseline to week 24. The primary efficacy analysis was performed on the intent-to-treat (ITT) population. A 2-sided 95% confidence interval (CI) was used to establish non-inferiority of MYL IG to Lantus. A repeated measures analysis employing a restricted maximum likelihood-based, mixed effects model approach (MMRM) was used to produce a 95% CI for the difference between MYL IG and Lantus for mean change of HbA1c at week 24. The MMRM model included the fixed, categorical effect of treatment group assignment, visit, treatment group-by-visit interaction, and the other fixed-effect terms of region, basal insulin dosing time, and baseline HbA1c value as covariates. The data collected at baseline, Week 12, and Week 24 was used in the MMRM model for the interim analysis. For patients who prematurely withdrew from the study, if the last post-baseline data was not collected at a scheduled visit, then it was mapped to the next scheduled visit and that data was included in the analysis. Non-inferiority of MYL IG to Lantus was established if the upper bound of the 95% CI was no greater than 0.4% at 24 weeks. The least squares (LS) means for each treatment group and associated standard errors were derived. Differences in LS means were calculated as associated 2-sided 95% CI. A further robustness check was conducted on the primary efficacy variable using the per-protocol (PP) population and applied the same MMRM procedure to establish non-inferiority. Other sensitivity analyses were also used to check robustness of primary analysis method. The secondary efficacy analyses were performed on the IIT population. Similar statistical analysis approach for primary variable was performed for all secondary continuous variables. The secondary variables included HbA1c change from baseline at scheduled visits, change in fasting plasma glucose from baseline at scheduled visits, changes in SMBG levels from baseline at scheduled visits, changes in daily insulin dose unit/body weight (mealtime insulin, basal insulin, and total insulin) from baseline at scheduled visits. Furthermore, the percentage of patients reaching the target HbA1c (<7%) was summarized, and compared by treatment using the Cochran-Mantel–Haenszel test with basal insulin dosing time as stratification factor. Contrasts of LS mean at each scheduled visit was used to evaluate all pairwise treatment comparisons, and 95% confidence intervals for treatment differences in LS means were computed for each visit. The secondary safety analyses were performed on the safety population and similar analysis methods of secondary efficacy analysis for continuous variables were also used. The secondary safety variables included hypoglycaemic rate, antibody specific bindings, vital sign, and laboratory measurements. For safety categorical data analyses such as incidence of AEs, incidences of hypoglycaemic events, and incidences of total anti-drug antibody (ADA) and cross-reactive insulin anti-body, Fisher's exact test or Chi-squared test were used.

An interim database lock was conducted after all the patients were exposed to 24 weeks of treatment (completed visit 17). Following the interim database lock, an interim analysis corresponding to the primary analysis was planned and performed. The results of the interim analysis are kept confidential and have not been communicated to the study centers except one investigator for reviewing the CSR.

Results

For details on subject disposition, treatment compliance and baseline characteristics please refer to the Clinical AR.

Primary efficacy parameter: change in HbA1c from baseline to Week 24

The LS mean difference at **Week 24** (primary endpoint) between the two groups was 0.03% (SE, 0.046) and the 95% CI was -0.066% to 0.117%, and was within the pre-defined non-inferiority margin of 0.4%. The primary efficacy analysis (non-inferiority test for change in HbA1c from baseline to week 24) for the ITT population, the results of sensitivity analyses performed using the PP population and the results of sensitivity analyses investigating the impact of missing data are summarized in the following table:

Table: Statistical Analysis of Change in HbA1c (%) from Baseline to Week 24 – Primary Analysis Non-Inferiority Test and Sensitivity Analyses

Model	Method	Population	LS Means Difference (SE)	95% CI for LS Means Difference
MMRM	Primary Analysis (NI)	ITT	0.03 (0.046)	(-0.066, 0.117)
MMRM	NI	PP	0.02 (0.047)	(-0.073, 0.110)
	Multiple Imputation, Adjusted for NI Margin	ITT	0.04 (0.047)	(-0.050, 0.134)
		PP	0.02 (0.047)	(-0.067, 0.117)
	Multiple Imputation	ITT	0.03 (0.047)	(-0.064, 0.119)
		PP	0.02 (0.047)	(-0.073, 0.111)
ANCOVA	LOCF	ITT	0.03 (0.047)	(-0.061, 0.121)
		PP	0.02 (0.047)	(-0.068, 0.116)

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HbA1c, glycosylated hemoglobin; ITT, intent to treat; LOCF, last observation carried forward; LS, least squares; MMRM, mixed-effects model repeat measurement; NI, non-inferiority; PP, per protocol; SE, standard error.

After **Week 52**, the LS mean difference in HbA1c between the two groups was -0.05% (SD, 0.052) and the 95% CI was -0.148% to 0.057%, again within the non-inferiority margin of 0.4%, see table below.

Table: Statistical Analysis (MMRM) of Change in HbA1c (%) from Baseline to Week 52 – Sensitivity Analysis (ITT Population)

Treatment Group	n/N	LS Mean (SE)	95% CI	LS Means Difference (SE)	95% CI for LS Means Difference
MYL IG (N = 280)	278/280	0.21 (0.055)	(0.100, 0.306)	-	-
Lantus (N = 277)	274/277	0.25 (0.056)	(0.144, 0.363)	-	-
MYL IG - Lantus	-	-	-	-0.05 (0.052)	(-0.148, 0.057)

Abbreviations: CI = confidence interval; HbA1c = glycosylated hemoglobin; ITT = Intent-to-Treat; LS = least squares MMRM = Mixed-Effect Repeated Measure model; MYL IG = Mylan's Insulin glargine; N = number of patients assessed in ITT Population; n = number of patients with changed HbA1c from Baseline to Week 24; SE = standard error
The MMRM model is Change from baseline HbA1c = Treatment + Visit + Region + Basal insulin dosing time + Treatment * Visit + Baseline HbA1c.
Non-inferiority of Mylan's Insulin glargine to Lantus is established if the upper bound of the 95% CI is no greater than 0.4%.

Secondary efficacy parameters

A clinically non-significant decrease in the mean **FPG** at Week 24 from baseline (-0.81 mmol/L; p=0.004) was observed for MYL IG; while there was a slight increase from baseline in Lantus group (0.09 mmol/L; p=0.745). There was a statistically significant difference between the two treatment groups (p=0.017) at Week 24. At Week 52, mean FPG increased from baseline by 0.23 mmol/L in the MYL IG and by 0.43 mmol/L in the Lantus group. The differences vs. baseline and the difference between the groups were not statistically significant.

The **SMBG profiles** were comparable between two treatment groups. The overall average mean for the change from baseline for SMBG at Week 24 was -0.078 for MYL IG and -0.095 for Lantus treatment group; the difference between groups was not statistically significant (p=0.893). At Week 52, the overall average mean change from baseline was -0.082 for both treatment groups.

At Week 24, there was no statistically significant difference in change from baseline between the two treatment groups for **mealtime and total daily insulin doses** (p=0.574 and p=0.567 respectively).

There was a statistically significant difference in change from baseline between treatment groups for **daily basal insulin dose** at Week 24 (p=0.002). At baseline, patients in MYL IG groups had lower daily basal insulin dose (0.3138 U/kg) compared to the patients in Lantus group (0.3289 U/kg). The mean change from baseline at Week 24 of daily basal dose for the MYL IG treatment group and the Lantus treatment group were 0.0152 U/kg and 0.0034 U/kg, respectively. During the course of the study, the basal insulin doses in both treatment groups converged leading to a similar basal insulin dose at Week 24. At Week 52, the mealtime insulin doses were still similar, 0.3795 vs. 0.3629 U/kg (MYL IG vs. Lantus). Basal insulin use still was numerically higher in the MYL IG group, 0.0128 vs. 0.0043 U/kg (MYL IG vs. Lantus); the difference was not statistically significant.

The **proportion of patients with HbA1c <7%** at Week 24 was comparable between the two treatment groups as there were 73 (26.1%) patients in the MYL IG treatment group and 84 (30.3%) patients in the Lantus treatment group. The difference between the two treatment groups was not statistically significant (p=0.250). At Week 52, 65 patients (23.2%) in the MYL IG and 61 patients (22.0%) in the Lantus group had an HbA1c below 7%.

2.5.1. Discussion on clinical efficacy

Design and conduct of clinical studies

The main focus of this application is to show that MYL-1501D (MYL-1501D, Glargine Mylan) is biosimilar to the reference product Lantus. The PK/PD clamp studies are therefore considered to be pivotal for the demonstration of equivalent efficacy. Efficacy data from clinical trials using HbA1c as endpoint are rather insensitive and can therefore only be considered supportive. No dose-finding studies have been performed which is acceptable for a biosimilar.

The efficacy profile of MYL-1501D was demonstrated based on 24-week data from a phase III clinical trial (study MYL-GAI-3001). This study was a randomized, open-label, 2-parallel group efficacy study comparing MYL1501D and Lantus in subjects with T1DM. Reduction of HbA1c from baseline after 24 weeks was the primary efficacy endpoint. The pre-specified non-inferiority margin of 0.4% has likewise been used in previous studies and is acceptable. Secondary efficacy endpoints, including SMBG profiles, insulin doses, the proportion of subjects achieving glycaemic goals and fasting plasma glucose (FPG) are commonplace in studies of anti-hyperglycaemic medications.

The study was conducted open–label, i.e. subjects, investigators and sponsor personnel were aware of subject treatment assignments, but laboratory personnel remained unaware. This is acceptable for comparing two injectables administered by patients such as insulin.

A supportive study (FFP-112-02) was conducted in Japanese T1DM patients using Lantus JP as reference investigational product. In general, the same design as in study MYL-GAI-3001 has been used; in this supportive study data at week 52 were also submitted.

Efficacy data

The treatment groups in study MYL-GAI-3001 were generally well-balanced and representative of the EU population. Equivalence was demonstrated between MYL1501D and Lantus for change from baseline in HbA1c at 24 weeks in patients with T1DM. Additional sensitivity analyses were performed on both ITT and PP populations with different methods and all demonstrated non-inferiority. Results from the secondary efficacy analyses (SMBG profiles, change from baseline in total and meal time insulin doses, proportion of

patients with HbA1c below 7%) supported similarity between MYL1501D and Lantus. The statistically significant difference at week 24 in FPG (with a slight decrease in FPG with MYL1501D and a slight increase with Lantus) is likely a chance finding and is not considered clinically relevant. The same applies for the difference in the mean change from baseline at week 24 for daily basal insulin dose between the two treatment groups (with a moderately greater increase in dose from baseline found for the MYL1501D group). The latter could at least partly be explained by a more intense titration due to a slightly lower baseline dose of basal insulin in the MYL1501 D group.

Results of the supportive study conducted in Japan (FFP-112-02) also showed similarity in antihyperglycaemic efficacy between the investigational insulin glargine and Lantus JP, which was maintained throughout week 52.

During the procedure, updated data for study MYL-GAI-3001, including results at week 52, has been submitted. Small errors in previously submitted results of the primary 24 wk analysis (HbA1c) and results of secondary endpoints slightly differed (to a clinically not relevant extent), due to a software error, and were corrected in this submission.

2.5.2. Conclusion on clinical efficacy

As the euglycaemic clamp PK/ PD studies are considered to be the most sensitive approach in establishing similar efficacy of two insulins claimed to be biosimilar, study MYL-GAI-3001 is considered only supportive with regard to efficacy in this application dossier. Equivalence with regard to HbA1c change from baseline at week 24 between MYL1501D and Lantus in patients with T2DM was demonstrated and this was achieved at similar week 24 total insulin doses. Antihyperglycaemic efficacy was maintained at week 52 with similar results across treatment groups. The results on the secondary endpoints generally support the primary outcome.

2.5.3. Clinical safety

The safety assessment is mainly based on the main, world-wide phase 3 trial MYL-GAI-3001 (3001 for short) in Type 1 diabetics. In this study, Lantus sourced in the United States (US) served as comparator. Pharmaceutical bridging studies were performed to address representativeness of US Lantus for EU Lanus (see quality part).

The other two completed phase 3 trials, CLG031/BIO012/DM/GLA/2007 (2007 for short) and FFP-112-02 (FFP-02 for short) were conducted outside Europe (India and Japan) and used formulations of Mylan's insulin glargine that differ from the formulation intended to be marketed. Furthermore, the comparator (Lantus) was sourced outside the EU, and no pharmaceutical bridging studies to EU Lantus were performed for these Asian Lantus preparations.

The supportive studies revealed no specific safety concern for Glargine Mylan. Hypoglycaemia was the most frequently reported AE type; the incidence of hypersensitivity reactions and injection site reactions was low and gave no hint for enhanced immunogenicity of Glargine Mylan. Since the Mylan preparations used in the supportive studies differed from the preparation intended for marketing and since Lantus sourced from outside EU was used without showing representativeness, the results regarding anti-insulin antibodies from these studies are considered not relevant for the present application. Safety aspects of the supportive studies will not be discussed in further detail.

Patient exposure

In Study 3001, 558 patients were evaluated for safety, 280 in the Mylan and 278 in the Lantus group. Through Week 52, the mean exposure of patients exposed to MYL IG was 351.0 days (SD: 60.07) and to Lantus was 348.6 days (SD: 70.74).

Adverse events

The following table provides an overview of the AE incidence in Study 3001 (52 week data). 80.4% and 86.0% in the Mylan and Lantus group, respectively, had at least one AE (mainly hypoglycaemia). 6.4% in the Mylan and 7.9% in the Lantus group had at least an SAE. Also in the other AE categories shown below no remarkable differences between Mylan and Lantus were observed.

Table: Overview of Treatment-Emergent AEs (Safety Population)

Category	MYL IG (N = 280)		Lantus (N = 278)		Total (N = 558)		p-value
	n (%)	e	n (%)	e	n (%)	e	
Number of patients with •≥1 TEAE	225 (80.4)	3589	239 (86.0)	3718	464 (83.2)	7307	0.076
Number of patients with • ≥1 SAE	18 (6.4)	26	22 (7.9)	37	40 (7.2)	63	0.497
Number of patients with • ≥1 treatment-related TEAE	122 (43.6)	2419	122 (43.9)	2280	244 (43.7)	4699	0.941
Number of patients with • ≥1 TEAE of Grade 3 or Higher	23 (8.2)	38	23 (8.3)	35	46 (8.2)	73	0.980
Number of patients with ≥• 1 treatment-related SAE	2 (0.7)	2	3 (1.1)	3	5 (0.9)	5	0.685
Number of patients who discontinued the study due to TEAE	3 (1.1)	4	3 (1.1)	3	6 (1.1)	7	> 0.999
Number of patients who died	2 (0.7)	7	1 (0.4)	1	3 (0.5)	8	> 0.999
Number of patients with • ≥1 local and systemic reactions	5 (1.8)	9	6 (2.2)	6	11 (2.0)	15	0.752

MYL IG = Mylan's insulin glargine

Far the most AEs were hypoglycaemias. Otherwise, respiratory and urinary tract infections were rather frequent. There was a numerical imbalance for nasopharyngitis and for headache (both were more frequent in the Lantus group), but this is most likely a chance finding and not related to study medication. In general, the frequencies of the different AE types were similar in the Mylan and Lantus group.

Hypoglycaemia

All hypoglycaemia

Hypoglycaemia rate per patient per 30 days calculated between two visits is defined as total number of episodes between two visits divided by the number of days between the visits, multiplied by 30 days. The hypoglycaemic rates include severe hypoglycaemia, documented symptomatic hypoglycaemia, asymptomatic hypoglycaemia, probable symptomatic hypoglycaemia, relative hypoglycaemia, and nocturnal hypoglycaemia. The number of events especially of asymptomatic hypoglycaemia is dependent on how extensively the blood glucose was monitored which was different throughout the study. To ensure appropriate titration, during the run-in period and the first 4 weeks post randomization, eight point SMBG was performed three days a week every week, while after Week 4, it was performed at 4 week interval.

Asymptomatic hypoglycaemia was defined as an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).

Overall constant profiles of hypoglycaemic rate were observed in both treatment groups at both run-in and treatment periods (see figure below). At baseline mean actual rates were 7.849 (episodes/30 days) in MYL IG treatment group and 7.462 (episodes/30 days) in Lantus treatment group. The mean values of actual rate were 2.852 versus 2.661 (episodes/30 days) at Week 24 and 1.739 versus 1.732 episodes/30 days at Week 52 in MYL IG and Lantus groups respectively.

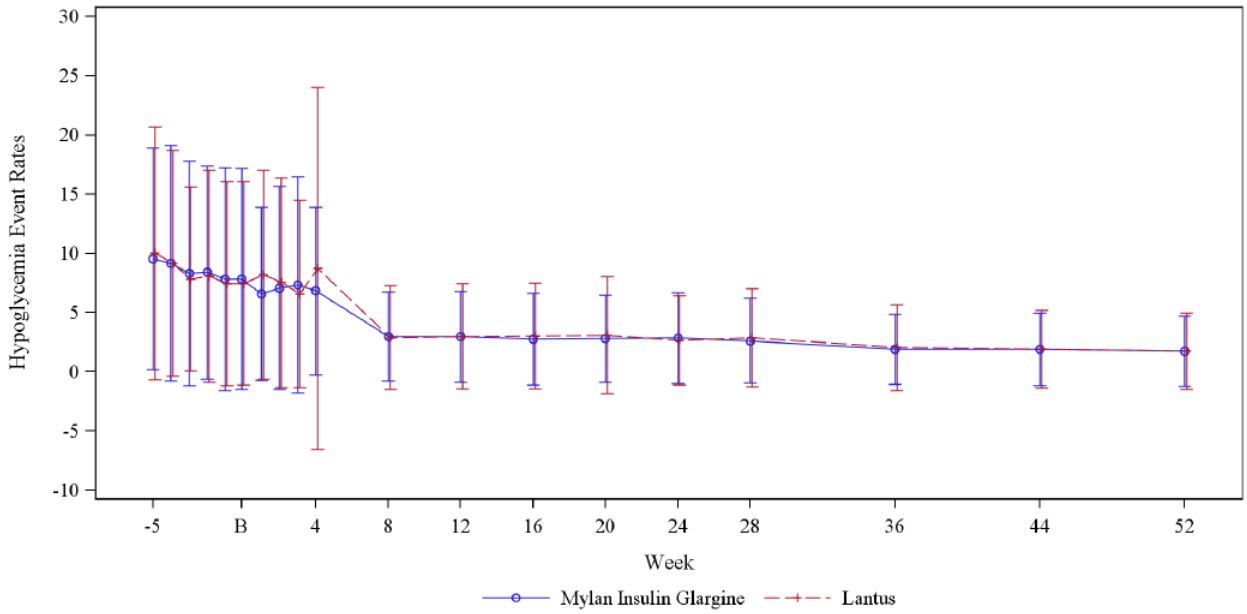


Figure: Mean (±SD) Graph for the Actual Hypoglycaemia Event Rates (Episodes/30 Days) by Visit and Treatment Safety Population

Nocturnal hypoglycaemia

Similar to anytime hypoglycaemic profiles, the nocturnal hypoglycaemia event rates were also comparable between the two treatment groups. At baseline, mean actual nocturnal rates were 1.555 (episodes/30 days) in MYL IG treatment group and 1.368 (episodes/30 days) in Lantus treatment group. The mean values of actual rate were 0.538 versus 0.404 (episodes/30 days) at Week 24 and 0.238 versus 0.264 (episodes/30 days) at Week 52 in MYL IG and Lantus treatment groups, respectively (see figure below).

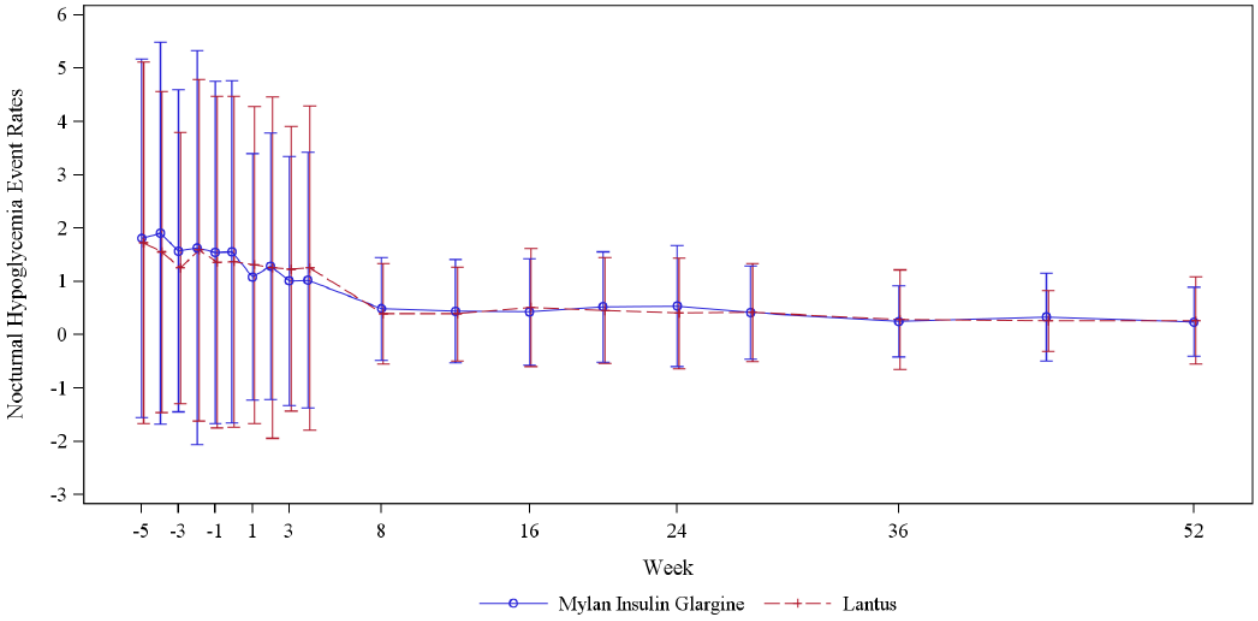


Figure: Mean (±SD) Graph for the Actual **Nocturnal** Hypoglycaemia Event Rates (Episodes/30 Days) by Visit and Treatment Safety Population

Severe hypoglycaemia

An event was considered severe hypoglycaemia if it required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions which resulted in neurological recovery, regardless of the availability of a blood glucose measurement.

Incidence of severe hypoglycaemic events was rare in both treatment groups. Similar incidences were reported in both treatment groups at scheduled visits. Of 11 patients with a severe hypoglycaemic event in **MYL IG** treatment group, 8 (**2.9%**) patients reported at least one severe hypoglycaemic event at night time while 7 (**2.5%**) patients reported at least one severe hypoglycaemic events at night time in **Lantus** treatment group.

Serious adverse events and deaths

Three patients died in Study 3001:

- Patient 0020602 (Lantus group), a 61-year old Caucasian male, had a myocardial infarction on Day 50 of treatment. The investigator considered the event to be unrelated to study drug. The patient died on Day 62 of treatment. An autopsy was not performed
- Patient 1103403 (MYL IG group), a 42-year old male, experienced the SAE of hypoglycaemia on Day 70 of treatment. The investigator considered the event to be probably related to study drug. The patient died on the same day. An autopsy was not performed.
- Patient 1102105 (MYL IG treatment group), a 65-year-old female, died on Day 347 of treatment due to unknown aetiology. The event of death was considered unlikely related to the study medication. An autopsy was not performed.

Hypoglycaemia reflects an exaggerated PD effect of insulin. Therefore, the respective fatal event does not indicate a safety concern for Mylan's insulin glargine.

SAEs in Study 3001

A total of 40 (7.2%) patients (18 [**6.4%**] versus 22 [**7.9%**] in MYL IG and Lantus treatment group, respectively) experienced at least one TESAE. The highest incidence of SAEs overall was observed for metabolism and nutrition disorders SOC; 7 (2.5%) patients and 10 (3.6%) patients in MYL IG and Lantus treatment groups, respectively. At the preferred term level, **hypoglycaemia** occurred with the highest frequency; 8 events the in MYL IG treatment group and 16 events in the Lantus treatment group. Generalized tonic-clonic seizure and goiter, each experienced by 2 patients in the Lantus treatment group, and acute kidney injury, experienced by 2 patients in the MYL IG treatment group, were the only other SAE PTs reported for more than 1 patient.

Laboratory findings

There were no meaningful changes in the mean values of the standard haematology and clinical chemistry parameters obtained. Some patients displayed individual clinically significant abnormalities; e.g., three patients in the Lantus group had low neutrophil or platelet count at a certain visit. Regarding serum chemistry, there were isolated changes in laboratory values at various time points but there was no consistent trend and there was no difference in the treatment groups. There were no patients with marked abnormal laboratory criteria in urinalysis parameters reported in this study.

Vital signs: There were no clinically meaningful changes in mean values from baseline to Week 12, Week 24, or Week 52 of the study for vital signs within the treatment groups. No clinically relevant treatment group differences were noted in the mean change from baseline for any vital signs.

Safety in special populations

Investigating safety in special populations in not required for a biosimilar application and hence was not done by the applicant.

Immunological events

Potential immunological effects of insulin are assessed based on injection site reactions, hypersensitivity reactions and formation of anti-insulin antibodies (incidence and semi-quantitative plasma level). Note that anti-insulin antibodies will be called anti-drug antibodies (ADA) in the following.

Study 3001

Injection site reactions

No injection site reactions were reported.

Hypersensitivity reactions

The following table summarises the observed potential hypersensitivity reactions in the Mylan and Lantus group. The number of events was low, and no meaningful differences between Mylan and Lantus became obvious.

Table: Local and Systemic Allergic Reactions in Patients (Safety Population)

Category (Preferred Term)	MYL IG (N = 280) n (%)	Lantus (N = 278) n (%)	Total (N = 558) n (%)
Number of patients with local/systemic allergic reactions	5 (1.8)	6 (2.2)	11 (2.0)

Local	3 (1.1)	4 (1.4)	7 (1.3)
Dermatitis contact	0	3 (1.1)	3 (0.5)
Eczema	1 (0.4)	0	1 (0.2)
Rash	1 (0.4)	0	1 (0.2)
Seasonal allergy	1 (0.4)	1 (0.4)	2 (0.4)
Systemic	2 (0.7)	2 (0.7)	4 (0.7)
Dermatitis allergic	1 (0.4)	0	1 (0.2)
Food allergy	0	1 (0.4)	1 (0.2)
Glomerulonephritis minimal lesion	1 (0.4) [a]	0	1 (0.2)
Peripheral swelling	1 (0.4) [a]	0	1 (0.2)
Seasonal allergy	0	1 (0.4)	1 (0.2)
Swelling face	1 (0.4)[a]	0	1 (0.2)

Anti-drug antibodies (ADA)

Method:

The analytical method uses a radioimmunoprecipitation assay (RIPA) format. Positive controls (PC) were prepared by spiking guinea pig anti-Lantus/Mylan Insulin Glargine (anti-LAN/MIG antibody) into the negative control (NC) serum pool. Samples underwent acid dissociation to release any anti-insulin antibodies complexed with free drug, followed with charcoal absorption of the free insulin analogue. The treated samples were neutralized with Tris buffer and centrifuged to sediment the charcoal. The supernatant was incubated at 2 to 8°C overnight with the corresponding [125I]-labelled tracer under the following conditions for both MIG and LAN tracers:

- RIPA Assay Buffer only
- RIPA Assay Buffer with excess unlabelled MIG
- RIPA Assay Buffer with excess unlabelled LAN
- RIPA Assay Buffer with excess unlabelled Novolin R (NOV; fast acting human insulin produced by Novo Nordisk)

Positive Controls were prepared by spiking the pool of antibody-negative sera with guinea pig anti-Lantus/Mylan insulin glargine antibody supplied by Biocon Research Ltd at a concentration of 0.67 mg/mL.

After an overnight incubation, bovine gamma globulin and polyethylene glycol (PEG) were added to facilitate precipitation of antibody-tracer complex, centrifuged, and the supernatant was removed. The pellet was washed with PEG solution, vortexed, and centrifuged to re-precipitate the pellet. The supernatant was removed, and the pellet was counted on a gamma counter. A set of tubes that contained radiolabelled MIG or LAN was used to measure the total counts for the assay. The counts per minute (CPM) generated were used to calculate the % binding (%B/T) relative to the total CPM. Specific binding (%S/B = the difference between the %B/T for the uninhibited and the inhibited) and drug specific binding were reported.

Two radio immunoprecipitation assays, the MYL IG assay and Lantus assay, were employed for the assessment of ADA in each patient samples. A two assay approach was utilized due to the potential structural differences between drug products arising from the different host cells used in production. For each sample, the presence of antidrug antibodies was reported as Total ADA (positive or negative) with the percent specific binding response. Analogous to titre values, the %SB represents was the relative amount of antibody present in the samples. Antibodies cross reactive to human insulin were also reported in terms of their presence (positive or negative) and relative amount (%SB). The Total ADA in samples (if

present) were also characterised in terms of cross reactivity between drug products (MYL IG and Lantus), which is reported as Drug Specific ADA. This assessment was the difference in %B/T in a sample inhibited with an excess of each drug product in the same assay.

In order to avoid interference of the ADA assay with the therapeutically administered insulin present in plasma, the assay protocol requires liberation of the plasma insulin from the antibodies by acid treatment before performing the RIPA. Experiments performed for validation of this step demonstrated that removal of glargine from the ligand could be achieved (although not complete) and that the acid treatment did not interfere with further steps of the ADA assay. For assay validation, guinea pig anti-insulin antibody without insulin ligand was dissolved in normal human serum and used as positive control.

Results

Semi-quantitative antibody results, obtained instead of titres, are expressed as % specific binding (%SB) towards cross-reacting anti-drug antibodies (ADA). Specific binding and cross-reactivity are defined and determined as follows:

%SB means percent of specific binding. Specific binding usually refers to so-called cross-reactive antibodies.

Specific binding is defined as bound tracer (radioactively labelled MYL-GAI or Lantus) in the absence of unlabelled insulin minus bound tracer in the presence of a high surplus of unlabelled insulin. The unlabelled insulin occupies all specific binding sites for insulin so that the remaining binding of tracer must be unspecific and hence is subtracted to yield specific binding only.

Cross-reactivity means that the unlabelled insulin used for competition is human insulin instead of glargine. Thus, this approach only detects antibodies which also can bind human insulin, not only glargine.

When the same compound was used for tracing and competition, this was called "Total ADA" by the applicant. Patient serum samples were tested in both assays (one employed labelled MYL-GAI, and the other employed labelled Lantus) in a blinded format).

No major differences are expected between the total ADA and the cross-reacting ADA results since most ADA most likely bind various insulins since the molecular differences between the different insulins discussed here are small. As outlined above, two different tracers were used, MYL GAI and Lantus. The applicant has demonstrated that both tracers yielded very similar results, the applicant also demonstrated that all detected ADA reacted with MYL GAI as well as with Lantus.

The figure below shows the time course of ADA level (measures as %SB) over 52 weeks in the Mylan (blue) and Lantus (red) group of Study 3001. Data are expressed as change from baseline. Baseline level was around 10% SB in both groups. Given the high variability of the results, identified by large error bars, essentially no change over time became obvious. For Glargine Mylan, all data points were numerically below zero, indicating that ADA level had decreased, but the effect size us small so that no further conclusion can be drawn from this observation.

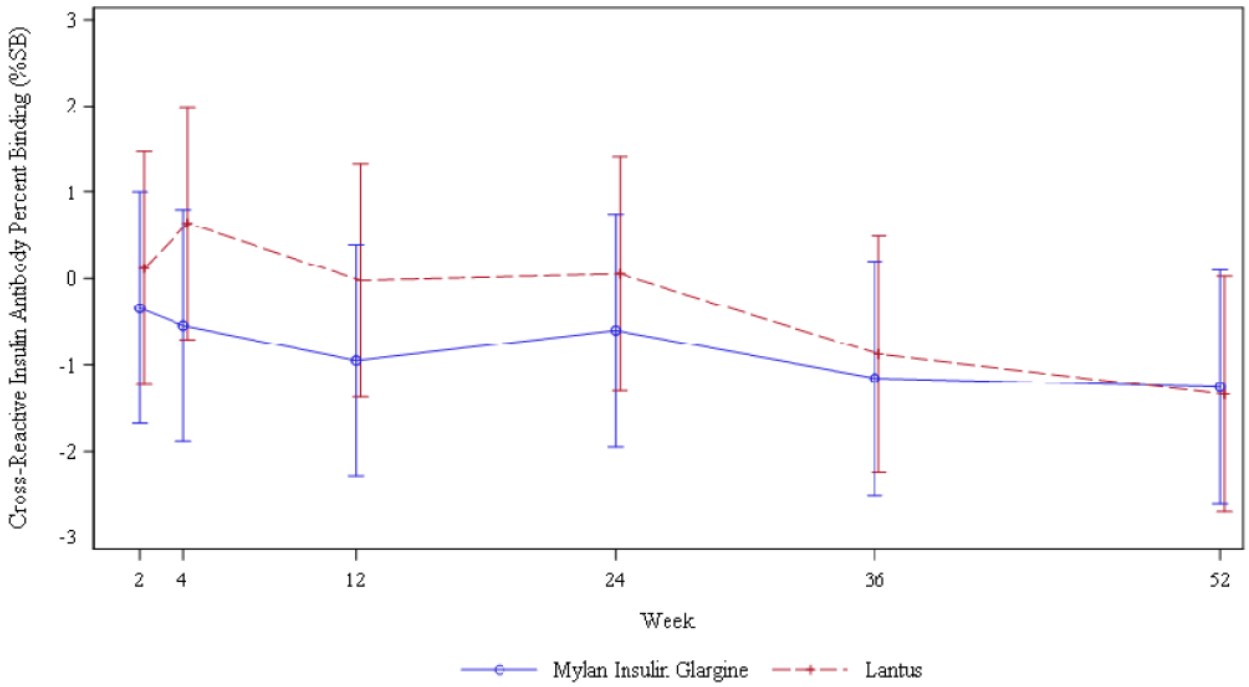


Figure: LS Means and CI for the Change from Baseline Cross-Reactive Insulin Antibody Percent Binding (%SB) Over Time by Treatment for MIG Assay Safety Population. Note: At baseline, %SB was around 10 in the MYL GAI and in the Lantus group (taken from Figure 14.4.7 of Study Report 3001).

The ADA incidence, expressed as percentage of patients affected, is listed in the following table. It became obvious that the percentage of (total) ADA-positive patients was highest at baseline and was always lower during the course of the study. The reason is unclear, but the finding is in line with the %SB results shown above.

The evaluation of cross-reacting ADAs revealed similar results (not shown here).

Table: Summary of Total Anti-Drug Antibody Response (ADA positive) for MYL IG and Lantus Assay (Safety population)

	MYL IG Assay			**Lantus Assay**		
Visit	**MYL IG (N=280) n (%)**	**Lantus (N=278) n (%)**	**p-value**	**MYL IG (N=280) n (%)**	**Lantus (N=278) n (%)**	**p-value**
Baseline	205 (73.2)	205 (73.7)	0.923	209 (74.6)	221 (79.5)	0.355
Week 2	193 (68.9)	199 (71.6)	0.626	201 (71.8)	204 (73.4)	0.617
Week 4	198 (70.7)	195 (70.1)	0.848	205 (73.2)	203 (73.0)	0.843
Week 12	204 (72.9)	200 (71.9)	>0.999	203 (72.5)	208 (74.8)	0.226
Week 24	194 (69.3)	197 (70.9)	0.765	209 (74.6)	206 (74.1)	0.834
Week 36	184 (65.7)	179 (64.4)	0.918	191 (68.2)	183 (65.8)	0.830
Week 52	190 (67.9)	185 (66.5)	0.833	196 (70.0)	190 (68.3)	>0.999

Neutralising antibodies were not determined *in vitro*. Instead, the applicant analysed whether there were clinical signs for neutralising ADA which can be identified by increasing insulin demand or deteriorating glucose control (e.g. HbA1c) in the absence of other reasons. Hence, the applicant provided scatter plots of daily insulin dose or HbA1c vs. ADA level where each data point represents an individual patient.

The plot for insulin dose is shown below. It can be derived from the plot that some patients required a rather high daily insulin dose, but the ADA level was low in these patients. Vice versa, patients with high ADA level had insulin doses in the usual range.

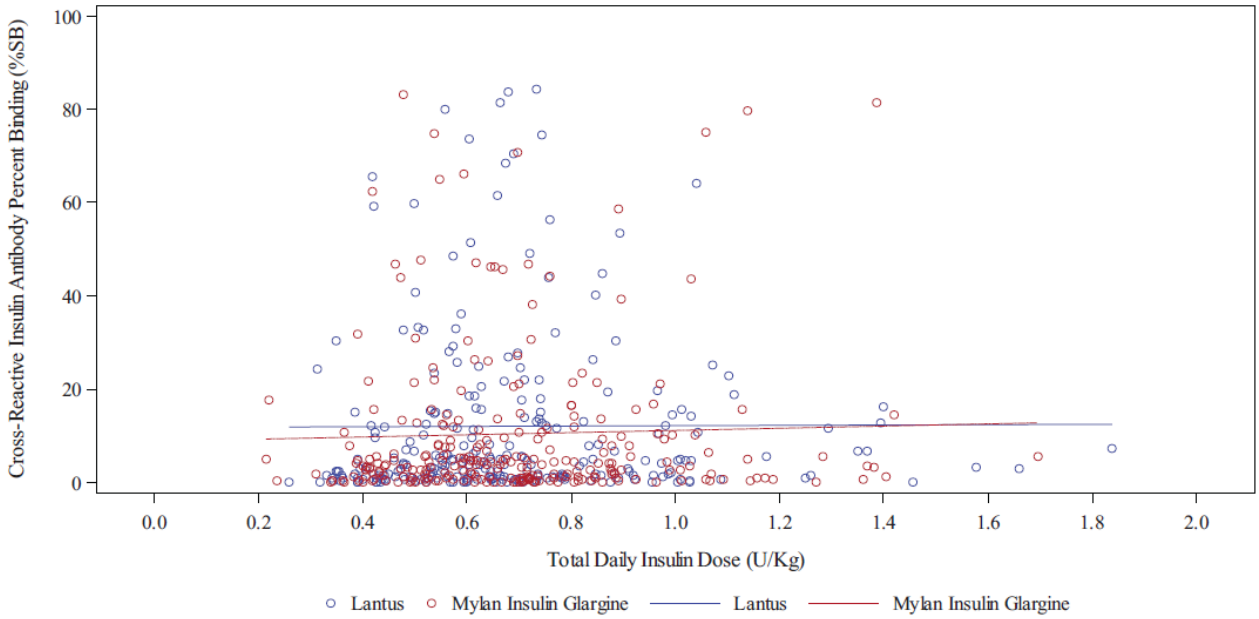


Figure: Scatter plot of Cross-Reactive Insulin Antibody Percent Binding (%SB) with Total Daily Insulin Dose (U/Kg) at Week 24 for MIG Assay Safety Population

The scatter plot showing HbA1c vs. ADA level is inserted below. There was no clear correlation between ADA level and HbA1c level, and there were no clear outlies which may identify patients with poor glycaemic control accompanied by high ADA level. The regression analysis of the Mylan group (red line) revealed a curve with a weakly positive slope. The slope is probably driven by three outlying data points: (1) HbA1c ≈9.6% / ADA level ≈40% SB; (2) HbA1c ≈10.0% / ADA ≈70%; (3) HbA1c ≈11.9% / ADA ≈22%. The applicant explained that the high HbA1c levels are most likely not due to neutralising ADA. Instead, two of the patients had frequent hypoglycaemias so that the insulin regimen was not tightened. One patient suffered from Hashimoto's thyroiditis the treatment of which probably has worsened glycaemic control.

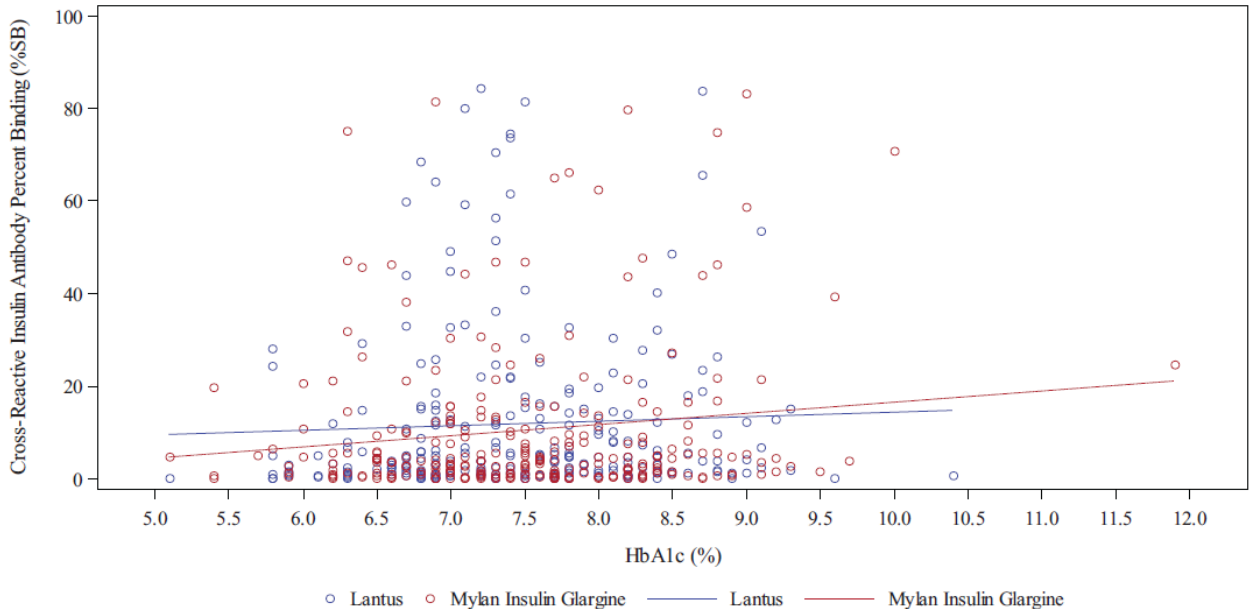


Figure: Scatter plot of Cross-Reactive Insulin Antibody Percent Binding (%SB) with HbA1c (%) at Week 24 for MIG Assay Safety Population

Safety related to drug-drug interactions and other interactions

Investigation of drug-drug interactions is not required for a biosimilar application and hence was not performed by the applicant.

Discontinuation due to AEs

A total of 6 (1.1%) patients in Study 3001 experienced 7 events leading to discontinuation of the study drug. Two patients in the Mylan group discontinued study drug due to hypoglycaemia. All other types of events occurred only once. For the latter events, relationship to study drug appears unlikely.

2.5.4. Discussion on clinical safety

Safety evaluation was mainly based on one phase 3 trial in T1DM patients which recruited patient worldwide including Europe, which used the current Glargine Mylan formulation and which employed US Lantus as comparator; for the latter, representativeness for EU-Lantus was addressed at the pharmaceutical level.

In a biosimilar application, safety assessment of the test product is mainly focussed on comparison to the reference product (Lantus) with respect to immunogenicity. General adverse events (AEs) and hypoglycaemia were also assessed and revealed no special safety concerns for Insulin Glargine Mylan. With regard to adverse drug reactions which are related to exaggerated pharmacological effects (e.g. hypoglycaemia), the demonstration of similar PK and PD profiles alone can already provide reasonable reassurance that these can be expected at similar frequencies. Results from the phase 3 study support the assumption of similar ADR profiles of test and reference.

The incidence of total AEs was similar between Glargine Mylan and Lantus; most AEs were hypoglycaemia. Serious AEs were infrequent with Glargine Mylan and Lantus.

Immunogenicity was assessed at three levels, injection site reactions, hypersensitivity reactions and formation of anti-drug antibodies (ADAs). The latter were characterised with respect to incidence and semi-quantitative plasma level (a substitute for titre).

Injection site reactions were not observed in the main phase 3 study; potential hypersensitivity reactions were infrequent and fairly balanced between the treatment groups. ADA incidences and plasma levels were similar between the Glargine Mylan and Lantus group. Thus, there was no hint for increased immunogenicity of Glargine Mylan from these observations.

Formation of antibodies against insulin is a well-known phenomenon in diabetics, especially with T1DM. Accordingly, most of the study patients had ADA already at baseline. Usually, anti-insulin antibodies are of no clinical relevance because they do not block the action of insulin (i.e. they are non-neutralising). Clinically relevant neutralising antibodies would lead to increased insulin need or to deteriorating glycaemic control. A total of four patients of the Glargine Mylan group had rather high insulin need or HbA1c and simultaneously higher ADA levels than most other patients. The applicant provided further information on these patients. The most likely reason for the rather poor glycaemic control was the high incidence of hypoglycaemic events in three of these patients. One patient had accompanying autoimmune disease the therapy of which most likely led to worsening of glycaemic control.

2.5.5. Conclusions on clinical safety

The phase 3 study in T1DM patients submitted by the applicant to investigate efficacy, safety and immunogenicity of Glargine Mylan is adequate. The study gave no evidence for safety concerns or increased immunogenicity of Glargine Mylan compared to the reference product Lantus.

2.6. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	· Hypoglycaemia · Hypersensitivity reactions · Injection site reactions
Important potential risks	· Hypoglycaemia caused by insulin mix-up · Malignancies · Immunogenicity · Underdosing due to Needle Blockage
Missing information	· None

Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to further characterise all safety concerns included in the RMP.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Hypoglycaemia	Text in SmPC: • Section 4.2 Posology and method of administration advises on safe transition from other insulins and cautions that intravenous administration could result in severe hypoglycaemia. • Section 4.4 Special warnings and precautions for use informs about this safety concern, describes relevant risk groups / risk factors, and recommends caution and intensified blood glucose monitoring in at-risk patients. • Section 4.5 Interaction with other medicinal products and other forms of interaction lists medicinal products whose concomitant use may cause hypoglycaemia. • Section 4.6 Fertility, pregnancy and lactation informs about increased risk of hypoglycaemia immediately after delivery. • Section 4.7 Effects on ability to drive and use machines contains information about possible effects of hypoglycaemia. • Section 4.8 Undesirable effects lists hypoglycaemia as a very common (≥1/10) adverse reaction to insulin, and informs that prolonged or severe hypoglycaemia may be life-threatening. • Section 4.9 Overdose warns that insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia. Other routine risk minimization measures: • The PL includes a detailed description of the risk of hypoglycaemia, risk factors for its occurrence, symptoms of hypoglycaemia symptoms, and guidance for the patient in case of occurrence of hypoglycaemia. • Prescription only medicine.	None
Important identified risk: Hypersensitivity	Text in SmPC:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
reactions	• Section 4.3 contraindicates use of the product in patients with hypersensitivity to the active substance or to any of the excipients. • Section 4.8 lists allergic reactions as a rarely (≥1/10,000 to <1/1,000) occurring undesirable effect and informs that such reactions may be life-threatening. <u>Other routine risk minimization measures:</u> • Prescription only medicine.	
Important identified risk: Injection site reactions	<u>Text in SmPC:</u> • Section 4.2 Posology and method of administration recommends rotation of the administration site. • Section 4.8 Undesirable effects lists injection site reactions and lipohypertrophy as common (≥1/100 to <1/10), and lipoatrophy as rare (≥1/10,000 to <1/1,000) adverse reactions. <u>Other routine risk minimization measures:</u> • Prescription only medicine.	None
Important potential risk: Hypoglycaemia Caused by Insulin Mix-Up	<u>Text in SmPC:</u> • Section 4.4 Special warnings and precautions for use, and Section 6.6 Special precautions for disposal and other handling advise that the label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins. <u>Other routine risk minimization measures:</u> • Prescription only medicine. • PL advises to check the product label before each injection to avoid mix-ups and includes detailed information about warning symptoms of hypoglycaemia as well as guidance to patients in case hypoglycaemia occurs.	None
Important potential risk: Malignancies	<u>Text in SmPC:</u> • The SmPC currently does not include any language in regard to this hypothetical risk. This is considered acceptable in light of the fact that the predominant opinion in the scientific and regulatory community (endorsed, e.g., by the CHMP) is that there is no convincing evidence for a carcinogenic role of insulin glargine or any other insulin derivative currently used	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	in diabetes therapy (see section SVII.3). Other routine risk minimization measures: • Prescription only medicine.	
Important potential risk: Immunogenicity	Text in SmPC: • Section 4.4 Special warnings and precautions for use of the SmPC informs that administration may cause insulin antibodies to form, which may necessitate adjustment of the insulin dose. Other routine risk minimization measures: • Prescription only medicine.	None
Important potential risk: Underdosing Due to Needle Blockage	Text in SmPC: • Section 4.2 Posology and method of administration requires that the instructions for use included in the package leaflet are carefully read before using the pre-filled pen • Section 4.4 Special warnings and precautions for use requires that instructions are provided to the patient on proper use of the product. Other routine risk minimization measures: • Prescription only medicine. • Availability of product as pre-filled pen formulation. • In the PL, clear and detailed instructions on the appropriate procedure for use of the product, including specific instructions on how to identify needle blockage and what to due if it occurs.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

2.7. Pharmacovigilance

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.

Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. User consultation

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

A non-dosing user handling assessment, conducted in accordance with IEC 62366-1:2015 and completed with the proposed commercial pen as part of the device design and development programme, confirmed that the MYL-1501D pen and the respective IFU are appropriate for use by the intended user population:

Summative Evaluation Study

The Summative Evaluation study was a non-dosing user handling assessment completed with the proposed commercial pen as part of the device design and development programme. The study was designed and conducted in accordance with IEC 62366-1:2015: Application of Usability Engineering to Medical Devices. The intent of the study was to confirm that intended users could use the pen safely and effectively using the commercial pen design and near final instructions for use (IFU). In the study, users were asked to simulate an injection using the pen into an injection surrogate. Users did not actually administer a dose of the drug. The primary objectives of the study were 1) to confirm that the MYL-1501D pen, when used in accordance with the IFU, could be used safely and effectively by the intended user population (diabetic patients, caregivers and healthcare professionals (HCPs)) and 2) to perform an assessment of use errors relating to any aspect of use of the pen or IFU. Overall, the number of use errors was low. The majority of use errors occurred in untrained participants. As patients, in practice, will receive training before the first use of a new pen, it can be concluded that the likelihood of use errors with the MYL-1501D pen is low. Non-compliance with instructions to prime injection pen needles is one of the most common errors seen in the use of insulin pens. In this study, patients had transferred their habit not to prime the pen properly to the usability testing. Therefore, this use error is not considered specific for the MYL-1501D pen. Overall, the outcome of the study confirmed that the MYL-1501D pen and the respective IFU are appropriate for use by the intended user population.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Semglee contains insulin glargine and has been developed as a biosimilar. The EU reference product Lantus is indicated for the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above. The Company was seeking approval for the same indications as those approved for Lantus.

3.1.2. Available therapies and unmet medical need

In the development of a biosimilar product, there is no requirement to demonstrate benefit to the patient *per se* as this has been shown for the reference product. The benefits and risks are inferred from the similarity of the test product to the reference product in terms of quality, efficacy and safety.

The reason for development is thus not to fulfil an unmet medical need but to offer a comparable alternative to the reference product. The efficacy/safety studies in the development programme included patients with prior use of Lantus in combination with a rapidly acting insulin.

3.1.3. Main studies

The goal of a biosimilar development is the demonstration of analytical, functional and clinical similarity to the reference product in a comprehensive comparability exercise. Semglee was generally developed in line with EU biosimilarity guidelines and EMA scientific advice.

Quality: Demonstration of analytical similarity is the mainstay of any biosimilar development. The applicant has provided the expected extensive analytical similarity studies.

Nonclinical: In-vitro studies are the most important part of the non-clinical biosimilarity exercise since this approach is expected to yield the most accurate characterisation of insulin's action on its primary target, the insulin receptor (IR). All insulin effects observed in vivo are a consequence of the interaction of insulin (glargine here) with its cognate receptor. As requested by the European guideline on biosimilar insulins, receptor interaction testing was performed at three levels, i.e. binding to IR, activation of IR, measured as autophosphorylation, and functional consequences of activation. Binding and activation was determined separately for both IR isoforms IR-A and IR-B, and also for the IGF1 receptor. Mitogenic potential was determined in permanently cultured human tumour cells. Although not requested by the guideline, data on in-vivo pharmacology, toxicology and toxicokinetics were also provided.

Clinical: Euglycaemic clamp PK/ PD studies are considered the most sensitive approach in establishing similar efficacy of two insulins claimed to be biosimilar so that the clinical comparability exercise should focus on this type of studies. This dossier contains 2 clinical pharmacology studies, one of which compared Semglee with EU sourced Lantus.

1. GLARGCT100111 (pivotal, conducted by Mylan's co-development partner, Biocon) a double-blind, single-dose, 3-way crossover, phase 1 euglycaemic clamp PK/PD study in patients with type 1 diabetes mellitus. This study compared MYL-1501D (=Semglee) with Lantus sourced from US as well as with Lantus sourced from the EU.

2. FFP-112-01 (supportive, conducted by FUJIFILM Pharma Co., Ltd.), a double-blind, single-dose, two-period crossover, phase 1 euglycaemic clamp pharmacokinetic/pharmacodynamic (PK/PD) study in healthy Japanese male subjects. This study compared insulin glargine (MYL-1501D) with Lantus (Japan-sourced). The comparison of PK and PD effects was done following Japanese guidelines. This study was not sponsored by Mylan, and the Applicant submitted this study documentation only for informative purposes.

The applicant also performed a phase 3 clinical efficacy/safety study (MYL-GAI-3001), the efficacy data of which are considered supportive. This was an open-label, 52-week study in T1DM patients to compare therapeutic non-inferiority (margin 0.4%) of Mylan glargine to US-Lantus in respect to HbA1c. 280 patients were randomised into the Mylan glargine group and 278 patients into the Lantus-US group. More than 94% of randomised subjects completed the 24-week study period. 52-week efficacy and safety data were submitted during the MAA procedure.

Supportive phase 3 trials using slightly different Semglee preparations, Lantus sourced outside EU and conducted in non-European countries were also submitted.

The revised product-class specific 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) provides the possibility of waiving the phase 3 clinical trial.

3.2. Favourable effects

Favourable effects supporting the demonstration of biosimilarity to the reference product:

From a quality perspective:

The quality documentation provided in the Semglee marketing authorisation application is of acceptable quality. Semglee is manufactured in *Pichia pastoris* and therefore contains glycosylated variants whereas the EU reference product Lantus is manufactured in E. coli and therefore is not glycosylated. However, the glycosylated species in the test product have been largely reduced and will be specified at low levels. The extensive comparability exercise demonstrated analytical similarity. The residual very small amount of glycosylated variants in Semglee is not expected to have any effect on efficacy, safety or immunogenicity. In addition, analytical bridging was performed to compare the proposed biosimilar, EU Lantus reference product and US Lantus comparator. In general, the choice of the test and reference product batches seems appropriate taking into consideration quantity, representativeness and differences in age. An analytical bridge could be established between EU- and US-sourced reference product. Therefore, studies performed with the US reference product are also relevant for the present application.

From a non-clinical perspective:

The applicant's pharmacology programme for establishing biosimilarity of Semglee and Lantus (sourced from EU and US) was generally in line with the CHMP insulin biosimilar guideline. Binding to and activation of (i.e. autophosphorylation) the two insulin receptor (IR) isoforms, IR-A and IR-B, were tested as well as metabolic effects (glucose uptake, adipogenesis and inhibition of lipolysis). Binding and activation tests were also done with the IGF-1 receptor (IGF1R). Mitogenic activity was tested by testing proliferation of permanently cultured human osteosarcoma cell line Saos-2 in response to stimulation with Semglee and Lantus. All assays revealed similar potency of Semglee and Lantus with respect to the tested parameter.

From a clinical perspective:

In the pivotal Phase 1 PK/PD clamp study GLARGCT100111 in patients with T1DM, the point estimates [90% CIs] of treatment ratio for Semglee vs. Lantus EU for the primary PK parameters INS-C_{max} and

INS-AUC_{last} were 1.03 [0.97 to 1.10] and 1.01 [0.95 to 1.09], respectively, indicating similar pharmacokinetic profiles between Semglee vs. Lantus EU. The results, obtained with LC-MS/MS analyses, are supported by an ELISA-assay, though this ELISA-analysis was burdened by major shortcomings.

In the phase 3 study (MYL-GAI-3001), non-inferiority regarding change in HbA1c was demonstrated. The LS mean difference in change in HbA1c from baseline to week 24 between the Semglee and the Lantus group was 0.03% (SE, 0.046) and the 95% CI was -0.066% to 0.117%, and was within the pre-defined non-inferiority margin of 0.4%.

The results for the secondary efficacy endpoints including fasting plasma glucose (FPG) and SMPG profiles, the proportion of subjects achieving glycaemic goals, and changes in insulin dose were overall similar for Semglee and Lantus in study MYL-GAI-3001 and thus support the primary results.

3.3. Uncertainties and limitations about favourable effects

From the quality point of view, the claim of analytical similarity between the MYL1501D test product and the reference product Lantus approved in the EU as well as bridging between EU Lantus and US Lantus is supported. No uncertainties remain.

The LC-MS/MS assay used to determine the M1 metabolites of insulin glargine was quite insensitive (LLoQ = 0.2 ng/mL) which, however, was the usual sensitivity of this new glargine-specific assay at that time. This rather high LLoQ led to exclusion of about one third of subjects from the primary PK analysis. However, several sensitivity analyses were provided by the applicant, ranging from including all subjects to including only subjects with profiles that had a certain minimum of evaluable measurements and sensitivity analyses using different LLoQs. All these sensitivity analyses yielded similar conclusions and equivalence criteria were well met for all analyses. Thus, the PK results can be considered robust. Therefore, the PK results support a conclusion of biosimilarity.

Equivalence for PD data was not formally shown since post-hoc exclusion of GIR profiles with a low glucose infusion rate, i.e. $AUC_{GIR.0-30h} \leq 50$ h*mg/kg/min, is not acceptable. Although a blinded review of data with the possibility to exclude low GIR-profiles was pre-specified, the exact cut-off value was not. In addition, reviewers were blinded to sequence but not to subject ID. In contrast to the analysis excluding patients with low GIR profiles, the analysis not excluding the respective subjects failed to show equivalence for the primary PD endpoints $AUC_{GIR.0-30}$ and GIR_{max} (95% CIs 0.78 to 1.34 and 0.85 to 1.28, respectively).

Though demonstration of PD similarity formally failed by exceeding the 80-125% margins, it is acceptable to consider the PD endpoints as secondary endpoints since the respective requirements outlined in the biosimilar insulin guideline are met: similarity between MYL-1501D and EU-insulin glargine in respect to analytical characterisation and non-clinical in vitro tests using reliable functional assays has been established. Similarity at the analytical and functional level together with PK similarity makes it unlikely that the variability in the PD data reflects product-related dissimilarity.

Furthermore, the following findings show that overall PD data are robust and reasonably support PK data:

- the applicant provided additional sensitivity analyses that used different cut-off values for data exclusion (ranging from no exclusion to exclusion of profiles with AUCGIR$\leqslant$500 mg/kg/min). The resulting point estimates were similar and close to 1 for all analyses performed
- assuming normal distribution might have also been an alternative option. The analysis of non-log-transformed data from all subjects yielded results within the 80-125% margins.
- no evidence for induction of a bias by exclusion of low profiles could be identified.

- similar results were obtained for comparison of MYL-1501D vs. US-Lantus and EU-Lantus vs. US-Lantus.
- the PD results are in good agreement with the PK results.

In addition, absent or low insulin response (i.e. absent or low GIR requirement) was equally distributed between treatments and occurred inconsistently (usually in just 1 out of 3 clamps).

Taken together, there is no evidence that the PD analysis with the 95% confidence intervals for the MYL-1501D versus Lantus-EU comparison being outside the pre-specified 80% to 125% margins for both $AUCGIR_{0\text{-}30h}$ and GIR_{max} is due to true differences in PD-kinetics. The PD results can best be explained by intraindividual variability of study subjects.

The initial uncertainties are considered resolved.

3.4. Unfavourable effects

The ADR profile of insulin glargine is well-known, the most important risk being hypoglycaemia.

From a nonclinical perspective no issues which would suggest unfavourable effects unique to the test product have been identified.

From a clinical perspective, there were no relevant differences in the overall rate of TEAEs, SAEs, treatment discontinuations due to AEs, laboratory findings, hypoglycaemic events, injection site nor hypersensitivity reactions between the Semglee and Lantus treatment group in the phase 3 study. The adverse events captured mirrored those already described in the SmPC for Lantus.

In the phase 3 study MYL-GAI-3001 at least one TEAE was reported in 80.4% of patients in the Semglee group and 86.0% in the Lantus group. The percentage of patients with at least one serious AE was 6.4% in Semglee group and 7.9% in Lantus group.

The incidence of hypoglycaemia (all sub-categories) was not relevantly different between the Semglee and the Lantus treatment group. Up to Week 24, In the Semglee group, 2.84 episodes per 30 days occurred, and in the Lantus group 2.67 episodes/30d. 53.6% of the patients in the Semglee group and 58.3% of the patients in the Lantus group had at least one episode of hypoglycaemia. The percentage of patients reporting at least one severe hypoglycaemia was low and was similar in the Semglee group (2.9%, 8 patients) and the Lantus group (2.2%, 6 patients). Also up to Week 52 no relevant differences in hypoglycaemia incidence was observed. No injection site reactions were observed in this study. Potential hypersensitivity reactions were reported in 5 patients (1.8%) in the Semglee and 6 patients (2.2%) in the Lantus group (52 wk).

At baseline, around 73% of the study patients were positive for anti-drug antibodies (ADA). Over the 52-week period ADA incidence slightly decreased to the same extent in both treatment groups. The ADA levels, measured as % specific binding in the ELISA used by the applicant, also remained essentially constant during the study in both treatment groups. Since there was no increase in ADA incidence or level during the study, treatment-emergent ADA could not be determined. There were no clinical signs for neutralising antibodies; some patients had a rather poor glycaemic control but in these cases other reasons were more likely (e.g., a high incidence of hypoglycaemia prevented tightening of the insulin regimen).

3.5. Uncertainties and limitations about unfavourable effects

The antibody assay included a step for removal of bound ligand because otherwise antibody molecules with insulin attached cannot be detected in the RIPA assay used. Removal of bound ligand was incomplete so that the antibody level may be higher than reported. However, this is not considered a concern since this affects Glargine Mylan and comparator Lantus to the same extent. Furthermore, the therapeutic insulin level is low so that in most cases only a small fraction of antibodies is blocked by attached insulin.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Semglee was developed as biosimilar to Lantus (insulin glargine). Of note, the conclusion of biosimilarity is based on the totality-of-the-evidence of the comparability exercise.

Demonstration of structural and functional similarity is the foundation of any biosimilar development. Analytical results from comprehensive biosimilarity testing indicate that the products can be regarded as similar.

From a non-clinical perspective, similarity of Semglee and Lantus was shown in terms of in vitro functionality, mitogenesis, and of toxicological, toxicokinetic and local tolerance profiles. In-vitro results are the most important part of the non-clinical biosimilarity exercise since this approach is expected to yield the most accurate characterisation of insulin's action on its primary target. All insulin effects observed in vivo are a consequence of the interaction of insulin (glargine) with its cognate receptor. The results presented supported this similarity claim.

From the clinical point of view, the demonstration of PK/PD similarity in the euglycaemic clamp studies is considered key for concluding similar efficacy. Similar PK for test and reference could be concluded since several sensitivity analyses yielded consistent results and therefore suggest that the exclusion of patients due to the rather high Limit of Quantification (LoQ) of the assay did not bias the results. PD similarity on the other hand was not formally shown, most likely due to large intra-individual variability in response to insulin glargine resulting in single profiles of absent or low GIR requirements in some subjects. However, similarity at the analytical and functional level together with PK similarity makes it unlikely that the variability in the PD data reflects product-related dissimilarity. In such cases, PD endpoints may be considered secondary in line with the biosimilar insulin guideline. There is no indicator that the PD analysis with the 95% confidence intervals for the MYL-1501D versus Lantus-EU comparison being outside the pre-specified 80% to 125% margins for both $AUCGIR_{0\text{-}30h}$ and GIR_{max} is due to true differences in PD-kinetics. The PD results can best be explained by intraindividual variability of study subjects. PD data reasonably support the PK results.

Demonstration of similar glycaemic control with similar insulin doses within the phase 3 study supports biosimilarity. However, the phase 3 study is less sensitive for showing similar efficacy than the PK/PD study.

Adverse events can be expected to occur at similar frequencies. In the efficacy and safety study, no relevant differences were noted in the incidence of adverse events, including hypoglycaemic events.

The phase 3 study mainly serves to assess immunogenicity. No increase in the incidence and level of anti-drug antibodies (ADA) was observed in each treatment group of the phase 3 study. Injection site reactions and potential hypersensitivity reactions also gave no hint for increased immunogenicity of Semglee compared to Lantus. There were no hints for neutralising antibodies.

3.6.2. Balance of benefits and risks

Considering the totality of data from the comparability exercise, biosimilarity of Semglee to the comparator Lantus was shown. No risks of Semglee beyond the known effects of insulin glargine were detected.

In line with the biosimilar insulin guideline, extrapolation to intravenous use and all indications and age groups of the reference medicinal product is acceptable.

3.6.3. Additional considerations on the benefit-risk balance

Although PD similarity was not formally shown, the Applicant provided sound argument that convincing overall evidence for biosimilarity, particularly based on analytical and functional data, has been shown between test and reference. PD data reasonably supports the PK results and the overall conclusion on biosimilarity.

3.7. Conclusions

The overall B/R of Semglee is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Semglee 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 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.