10 November 2016
EMA/813309/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LUSDUNA

International non-proprietary name: insulin glargine

Procedure No. EMEA/H/C/004101/0000

Note

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

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List of abbreviations

14C-2DG	2-deoxy-D-glucose labeled with 14C
A1C	Hemoglobin A1c
A660	Absorbance at 660 nm
AAS	Atomic absorption spectrometry
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AEX	Anion Exchange Chromatography
AIA	Anti-insulin antibodies
ALP	Aspartate aminotransferase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
API	Active Pharmaceutical Ingredient
approx	Approximately
ASaT	All Subjects as Treated
ASR	All subjects randomized
AST	Aspartate transaminase
AU	absorbance units
AUC	Area under the concentration-time 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
Avg	Average
BLQ	Below the Limit of Quantitation
BMI	Body mass index
bp	base pairs
BP	Blood pressure
Ca	Calcium
CD	Circular Dichroism
CE	centrifugation
CEX-HPLC	Cation-exchange high-performance liquid chromatography
CFR	Code of Federal Regulations
CFU	Colony Forming Unit
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
CL	Confidence limit
cLDA	Constrained longitudinal data analysis
Cmax	Maximal concentration
CMC	Chemistry, Manufacturing, and Controls
CP	Combination product
CPB	Carboxypeptidase B
CPE	Cytopathic Effect
CPP	Critical Process Parameter

CQA	critical quality attribute
CRS	Chemical Reference Substance
CRU	Clinical research unit
CSR	Clinical study report
CU	concentration units
Curr. Ed	Current Edition
CV	column volume
CV	Coefficient of variation
Da	Dalton
DAO	Data as observed
DF	Diafiltration
dL	Deciliter
DLT	Dose Limiting Toxicity
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DOA	Duration of action
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Calorimetry
DSP	Downstream Process
E. coli	Escherichia coli
EC	Ethics Committee
EC50	Half-maximal effective concentration
ECG	Electrocardiogram
ECL	Electrochemiluminescence
eCRF	Electronic case report form
EDTA	Ethylenediamine-tetraacetic acid
EdU	5-ethynyl-2'-deoxyuridine
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMCV	Encephalomyocarditis Virus
EoP	End of Production
EP	European Pharmacopoeia
EPC	end-of-production cells
ERC	Ethical Review Committee
ERW	endotoxin reduced water
EU	Endotoxin units
EU-approved Lantus	Lantus approved for marketing in the European Union
F	Female
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOB	Functional Observational Battery
FPG	Fasting Plasma Glucose
FSE	First subject enrolled

FSG	Fingerstick glucose
FSH	Follicle-stimulating hormone
FT-IR	Fourier Transformation Infrared Spectrometry
GC	gas chromatography
GCP	Good Clinical Practice
GIR	Glucose infusion rate
GIRmax	Maximum glucose infusion rate
GLP	Good Laboratory Practice
GLUT4	Glucose transporter type 4
GM	Geometric mean
GMR	Geometric mean ratio
GSD	Geometric standard deviation
h	Hour
HA	Hypoglycemia assessment
HbA1c	Glycated hemoglobin
HCl	Hydrochloric Acid
HCP	Host Cell Proteins
HDPE	High-density polyethylene
HG	homogenisation
HMW	Higher Molecular Weight
HMWP	High Molecular Weight Protein
HPLC	High Performance Liquid Chromatography
HP-SEC	High pressure size exclusion chromatography
Hr	Hour
hrs	Hours
IB	inclusion body
IC50	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICP-AE	Inductively coupled plasma atomic emission
ID	Identification
IEC	Independent Ethics Committee
IEF	Isoelectric Focussing
IEP	Isoelectric point
IGF1	Insulin-like growth factor 1
IGF1R	Insulin-like growth factor 1 receptor
IM	Intramuscular
INAb	Insulin-neutralizing antibody
IND	Investigational New Drug
IP	Intraperitoneal
IPC	In-Process Tests
IR	Infrared
IR	Insulin receptor
IR-A	Insulin receptor, isoform A
IRB	Institutional Review Board
IR-B	Insulin receptor, isoform B

IU	International Unit
IV	Intravenous
K_D	Equilibrium binding constant
kDa	Kilodalton
KF	Karl-Fischer
kg	Kilogram
KOP	key operating parameter
KPA	key process attribute
LAL	Limulus Amoebocyte Lysate
LB	lysogeny broth
LCL	Lower confidence limit
LC-MS	Liquid Chromatography – Mass Spectrometry
LC-UV	Liquid chromatography with UV detection
LDPE	Low-density polyethylene
LLQ	Lower Limit of Quantitation
LOCF	Last observation carried forward
LOD	Limit of Detection
LOQ	Limit of Quantitation
LPM	liters per minute
LS means	Least squares means
M	Male
M&N	Miettinen and Nurminen
MAA	Marketing Authorisation Application
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MF 1	microfiltration-1
Mg	Magnesium
Mg	Milligram
mg	Milligram
mL	Milliliter
MLV	Murine Leukemia Virus
mM	Millimolar
MS	Mass spectrometry
MSD	Merck Sharp & Dohme Corp.
MSD	Meso Scale Discovery
MTD	Maximum Tolerated Dose
Mw	Molecular Weight
N/A	Not Applicable
NA	not available
NA	Not applicable
Nab	Neutralizing antibody
NEC	Not Elsewhere Classified
NIR	Near-Infrared Analysis
nm	Nanometer
nM	Nanomolar

NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NOR	Normal Operating Range
NPH	Neutral Protamine Hagedorn
OD	Optical Density
OOS	Out of Specification
OUR	oxygen uptake rate
PACMP	Post approval change management protocol
PAR	Proven Acceptable Range
PD	Pharmacodynamic
PDLC	Predefined limits of change
PGt	Pharmacogenetics
Ph. Eur.	European Pharmacopoeia
pI	Isoelectric Point
PK	Pharmacokinetic
PO	Oral
PP	Per-Protocol
ppm	Parts per million
PPQ	Process Performance Qualification
PRS	Primary reference standard
PRV	Pseudorabies Virus
psid	pounds per square inch (differential)
PTC	Patient telephone contact
QA	Quality Assurance
QC	Quality Control
qPCR	Quantitative polymerase chain reaction
rDNA	Ribosomal deoxyribonucleic acid
RH	Relative humidity
RMP	Reference medicinal product
RMP	Risk Management Plan
RP	Relative potency
RP-HPLC	Reverse Phase HPLC
RP-UPLC	Reverse-phase ultra-performance liquid chromatography
RRT	Relative retention time
RS	Reference Standard
RSD	Relative Standard Deviation
RT	Room Temperature
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SC	Subcutaneous
SCP	Single-chain precursor
SD	Standard Deviation
SDF	Spray dried formulation

SDS-PAGE	Sodium Dodecyl Sulphate - Polyacrylamide Gel Electrophoresis
SE	Standard error
SE(C)-HPLC	Size Exclusion HPLC
SMBG	Self-monitored blood glucose
SMQ	Standardized MedDRA Query
SOC	super optimal broth with catabolite repression
SOC	System organ class
Spec(s)	Specification(s)
SPR	Surface plasmon resonance
SST	System Suitability Test
STZ	Streptozotocin
T1DM	Type 1 Diabetes Mellitus
Tmax	Time to maximal concentration
TOST	Two one-sided tests
TRIS	Tris(hydroxymethyl) aminomethane
TSH	Thyroid-stimulating hormone
TV	Total variability
U	Unit
U/kg	Units/kilogram
U100	100 Units/milliliter
UCL	Upper confidence limit
UF	Ultrafiltration
ULN	Upper limit of normal
US	United States
US-approved Lantus	Lantus approved for marketing in the USA
USP	United States Pharmacopoeia
USP	Upstream Process
UV	Ultraviolet
UVA	Ultraviolet Radiation A
UVB	Ultraviolet Radiation B
UVR	Ultraviolet Radiation
w/v	weight per volume
w/v	Weight/volume
w/w	weight per weight
WBC	White blood (cell) count
WCB	Working Cell Bank
WFI	Water for Injections
WRS	Working reference standard
X-MuLV	Xenotropic Murine Leukemia Virus
YT	Yeast extract and tryptone

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Limited submitted on 4 December 2015 an application for Marketing authorisation to the European Medicines Agency (EMA) for Lusduna, 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.

Information on paediatric requirements

Not applicable.

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 21 July 2011, 16 February 2012, 20 November 2014 and 19 January 2015. 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 4 December 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 March 2016.
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 21 March 2016.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 1 April 2016.

- During the meeting on 28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 29 April 2016 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 July 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 August 2016 .
- During the PRAC meeting on 2 September 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP. The PRAC assessment Overview and Advice was sent to the applicant on 3 September 2016 .
- During the CHMP meeting on 15 September 2016, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 11 October 2016.
- During the meeting on 7-10 November 2016, 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 Lusduna on 10 November 2016.

2. Scientific discussion

2.1. Introduction

Type 1 and type 2 diabetes mellitus (T1DM and T2DM) are the most common disorders of carbohydrate metabolism. Effective glucose lowering substantially mitigates many of the health risks associated with diabetes mellitus. Pharmacologic insulin treatment is required for all patients with T1DM and many patients with T2DM for glycaemic control. Long-acting basal insulins have an important role in the treatment of patients with T1DM and T2DM. Insulin glargine is a recombinant human basal marketed globally under the name Lantus that provides ~24 hour coverage with a generally flat time action profile over this period. MK-1293 has been developed to be a biosimilar product to Lantus. As with all pharmacologic insulins, the dose of MK-1293 is individualized through glucose monitoring and titration to achieve clinical target effect.

Lantus is indicated for the treatment of type 1 and type 2 diabetes mellitus, of diabetes mellitus in adults, adolescents and children aged 2 years and above. The Company is seeking approval for the same indication as the one approved for Lantus. The MK-1293 development programme was designed to establish similarity of MK-1293 to both US-approved Lantus and EU-approved Lantus. The Phase I programme demonstrated pharmacokinetic (PK) and pharmacodynamic (PD) similarity between MK-1293 and Lantus in healthy subjects and subjects with T1DM. Two phase III trials have been conducted in subjects with T1DM and T2DM.

Note: Beside of the current product name Lusduna, the previous names MK-1293 and Insulin Glargine MSD will also be used in this document.

MK-1293 has been developed to be a biosimilar product to Lantus. MK-1293 has the same amino acid sequence as Lantus and, like Lantus, MK-1293 is produced in *E. coli*.

The development programme was in general conducted in line with regulatory guidance form the EMA. Especially, the *Guideline on on-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues* (EMEA/CHMP/BMWP/32775/2005-Rev.1) has been taken into account.

For a biosimilar medicinal product, it is required to show similarity with the reference product, not patient benefit per se. Biosimilarity for an insulin with its reference product is established via a head-to-head comparison of physicochemical and functional characteristics, time-concentration and time-action profiles in at least one glucose clamp study and, tentatively, a safety/immunogenicity study.

2.2. Quality aspects

2.2.1. Introduction

Lusduna was submitted as a similar biological medicinal product in accordance with Article 10(4) of Directive 2001/83/EC. The reference medicinal product is Lantus 100 unit/mL solution for injection (Sanofi Aventis Deutschland GmbH). The applicant also included a comparison of EU Lantus and US Lantus to support the use of US Lantus as comparator product in Phase I and Phase III studies.

Lusduna is a solution for injection containing 100 units/mL of insulin glargine as active substance.

Other ingredients are: zinc chloride, metacresol, glycerol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.
The product is available in a cartridge presented as a combination product with a disposable multiple-dose pen injector.

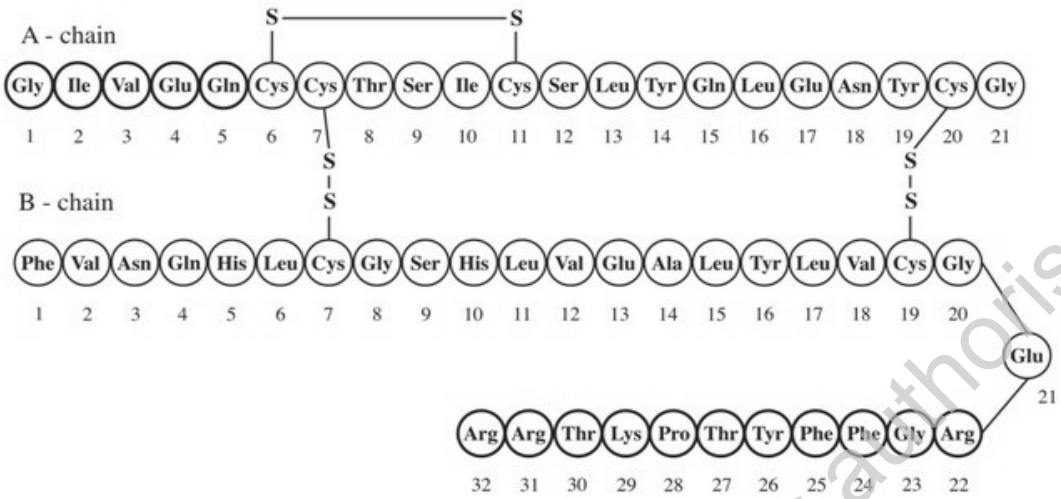
2.2.2. Active Substance

General Information

The active substance (MK-1293), recombinant insulin glargine, is a nonglycosylated two-chain polypeptide containing 53 amino acids, a 21 amino acid A-chain and a 32 amino acid B-chain. It is a structurally modified insulin analogue containing a C-terminal elongation of the B-chain by two arginine residues and a replacement of the asparagine residue on the C-terminal end of the A-chain by a glycine residue.

The A-chain and B-chain are linked via two disulphide bridges. In addition, the A-chain has one intra-chain disulphide bridge.

Figure 1 Amino Acid Sequence of MK-1293, Indicating Disulfide Bonds



Empirical Formula: $C_{267}H_{404}N_{72}O_{78}S_6$
Average Molecular Weight: 6063 Daltons
Monoisotopic Mass: 6059 Daltons

Manufacture, characterisation and process controls

The active substance is manufactured and released by Merck Sharp & Dohme in Elkton, Virginia, USA.

Description of manufacturing process and process controls

The manufacturing process is described in a detailed and comprehensive manner. The upstream process starts with a vial from the *E. coli* WCB that is expanded via shake flask, seed fermentation and production fermentation. Once the WCB vial cell suspension has grown to the required cell density in the shake flask it is transferred to the seed fermenter and cultivated until transfer to the production fermenter. During the batch phase of the production fermentation cells are further expanded to reach the necessary level to switch to the fed batch phase where λN17-proglargine expression is auto-induced in the fermentation production medium. The end of the fed batch phase is initiated with cooling of the fermentation broth as a preparation for primary recovery. λN17-proglargine is contained as intracellular inclusion bodies.

E. coli cells are harvested by centrifugation, washed and subsequently subjected to lysis to liberate the inclusion bodies. Inclusion bodies recovered by centrifugation represent the end of the upstream process and are stored as intermediate

The downstream process is initiated with solubilisation of inclusion bodies. Subsequent refolding takes place to allow the molecule to obtain its correct three-dimensional conformation with disulphide bridges correctly formed.

After chromatographic purification and enzymatic cleavage the product pool is precipitated, and the precipitate re-solubilised to improve the purity of the pool as by-products as well as host-related impurities (HCP and DNA) can be removed and reduced.

Two further chromatographic separation steps are performed to further increase product purity. The final elution pool is ultra-/diafiltrated to prepare the insulin glargine for crystallisation. Crystals that have formed are washed and dried on a filter dryer. The recovered active substance is packaged and stored at -20°C.

The upstream and downstream process is appropriately controlled by a set of process parameters. The process parameter ranges established as 'proven acceptable ranges' (PARs) are the result of extensive process characterisation studies performed as part of the process development.

A batch of insulin glargine is defined separately for upstream and downstream process.

Control of materials

MK-1293 is expressed as a fusion protein in *Escherichia coli* expression system. The host used for expression of λN17-proglargine is a mutant *E. coli* strain.

A two-tiered cell bank system, comprising MCB and WCB was established. Adequate release specifications and characterisation data of MCB and WCB were provided. Two Post Approval Change Management Protocols (PACMPs) were provided for establishment of future WCBs. The PACMPs were considered acceptable.

The limit of in-vitro cell age has been defined and is supported by results of end-of-production cells as well as upstream process batch data. Overall, the description of cell line development and establishment and maintenance of MCB and WCB is sufficiently detailed.

Control of critical steps and intermediates

The control strategy follows a risk based approach. Critical controls were defined based on experience from development and commercial scale manufacture supported by comprehensive process characterisation studies. These studies were performed to re-evaluate parameter ranges and confirm the criticality of process parameters and quality attributes. The applicant uses the terms key operational parameter (KOP) and key process attribute (KPA) to value the impact of the process on consistency and yield. As a result of process characterisation studies a detailed list of process parameters and in-process tests is derived to control the process.

Only one process intermediate, inclusion bodies, is defined throughout the manufacturing process and has been adequately supported by hold time studies and subsequent processing to active substance. Several hold points for intermediate steps are defined through upstream and downstream and all hold times claimed are adequately supported by cumulative hold time studies.

Process validation

The upstream and downstream manufacturing process was validated/verified by manufacturing batches of inclusion bodies (IBs) and active substance at the scale defined in the current batch definition.

A cumulative hold time study has been successfully performed both for the upstream and the downstream process and supports the hold times claimed. One process intermediate was defined, inclusion bodies, and the claimed hold time has been supported.

Lifetime studies for chromatography resins are performed on a concurrent basis at commercial scale. This is acceptable in view of the well-controlled process, and considering that an appropriate protocol has been submitted for the concurrent validation.

Transport of the active substance to the finished product manufacturing site has been adequately supported by shipping validation data.

Manufacturing process development

Process development was driven by the necessity to scale up and adapt the process to different facilities and by the aim to improve operability, productivity and robustness. Analytical comparability data of finished product manufactured with active substance from an earlier version of the process were comparable to finished product used in late stage development (based on active substance from a later version of the process). Overall, there were no drastic changes to the process and the applicant´s justification for only providing comparability data at the level of the finished product is acceptable given that the two main changes are improvements of the quality profile

The applicant also submitted a PACMP for an intended future commercial process. The applicant proposed to provide process comparability data as well as product comparability data in accordance to ICHQ5E to support the process changes. To support the proposed process changes small scale data will be provided with the post-approval variation. In addition, comparative extended characterisation as well as stability (accelerated, forced degradation) data will be provided.

Overall the manufacturing process development section is considered comprehensive and satisfactory, supporting the proposed control strategy.

Characterisation

Characterisation studies were performed with batches representative for the commercial active substance manufacturing process. Primary, secondary and tertiary structure has been studied in comparison to the USP and/or Ph. Eur. insulin glargine reference standards. Identical amino acid sequence of both chains, and an accurate molecular mass for the intact protein as well as for the two chains A and B were confirmed. The expected distribution of disulphide bridges as well as comparable secondary and tertiary structure profiles have also been confirmed for all batches tested.

The expected biological activity of MK-1293 active substance, i.e. activation of insulin receptor by tyrosine phosphorylation in HepG2 cells (pIR assay) and activation of Insulin-like Growth Factor-1 by tyrosine phosphorylation in HepG2 cells (pIGF-1R assay) was confirmed.

The product-related impurity profile of MSD insulin glargine was studied. Two impurity peaks were detected at >0.10% by RP-UPLC. These impurities were analysed for their biological activity.

Aggregates were measurable using HP-SEC in MK-1293 active substance batches at release. Dimer formation is a known insulin degradation pathway.

Evaluation of active substance stability under stress conditions have been presented as part of the analytical biosimilarity studies.

Specification

For active substance release and stability testing a specification has been provided that comprises identity testing by peptide map and UPLC, assay by UPLC and impurity testing. Residual host cell protein determination and host cell DNA determination is performed. In addition, bioburden and endotoxins are tested at active substance release and during stability, as appropriate. In general, the proposed specification is considered adequate.

Analytical methods

The analytical procedures indicated have been sufficiently and adequately described and sufficient details have been provided with regard to method validation. All proposed in-house analytical procedures were demonstrated to meet the defined validation requirements. Most of the analytical methods were developed before the Ph.Eur. Monograph “Insulin glargine” was published but are nevertheless considered acceptable. Particularly, one method was found more suitable than the pharmacopoeial method.

Batch analysis

Batch analysis data for active substance batches have been presented and the results confirm consistency of the manufacturing process. The acceptance limits included in the active substance specification have been set based on data obtained from batches that were included in clinical studies, process validation and stability studies. In general, the proposed approach to justify the active substance specifications is considered adequate and based on this the proposed acceptance limits seem reasonably deduced.

Reference materials

Sufficient details have been provided on the reference standard system established for active substance manufacture. Appropriate qualification protocols for future reference standards have been provided

Stability

Stability data has been provided for 36 months at the proposed long-term storage condition of -20°C/ambient humidity. Data was also provided for several batches for different storage times at accelerated and stress conditions. The proposed stability protocol containing adequate stability-indicating test parameters was considered appropriate.

The claimed active substance shelf life is supported by the stability data provided.

As light sensitivity of MK-1293 was confirmed on the finished product level, the active substance packaging was designed to protect from light.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

MK-1293 finished product is formulated as a sterile, clear colourless solution for injection with an insulin glargine target concentration of 100 units/mL corresponding to 3.64 mg/mL of MK-1293. The finished product is filled into a Ph. Eur. Type I glass cartridge and closed with a bromobutyl rubber stopper and an aluminium combi-seal which is fitted with a bromobutyl rubber. The product is presented as a combination product with a disposable, variable-dose, multiple-dose pen injector. The product is intended for subcutaneous injection. A target fill volume in the cartridge ensures a delivery of 3.0 mL by the pen.

The composition of MK-1293 finished product (as shown in Table 2) is similar to the composition of the reference product Lantus except for the content of glycerol. Several product formulation studies were conducted in order to evaluate the impact of excipients and attributes on MK-1293 stability. Finished product stability was mostly affected by storage temperature and pH leading to an increase of related proteins and aggregates at higher temperature and pH > 4.0. This observation resulted in establishing a formulation target pH of 4.0.

Table 2 Composition of MK-1293 finished product

Ingredient	Function
MK-1293	Active
Glycerol (85% w/v)	Inactive (excipient)
Zinc chloride	Inactive (excipient)
m-Cresol	Inactive (excipient)
Hydrochloride acid	Inactive (excipient)
Sodium hydroxide (1 N)	Inactive (excipient)
Water for injection	Inactive (excipient)

The manufacturing process was adequately developed. Parameters which may have a potential impact on product quality were evaluated in several process development studies. The studies focused on the compounding step, the filtration step and filling step. The acceptance limits or ranges established for the critical operational parameters of these steps were adequately evaluated in these studies and are confirmed to be adequate to ensure consistent product quality.

A list of relevant product development batches has been provided. Finished product lots produced at the commercial manufacturing site were used for clinical trials, stability studies and process validation studies. Except for an increase in batch size there was no further change in MK-1293 finished product production process after transferring the process to the commercial manufacturing site.

Based on the detailed description of pen-injector development and the studies performed for design verification and design validation, the chosen pen injector was found to be suitable and compatible with MK-1293 finished product to ensure a safe and accurate administration of product up to the end of shelf life. Furthermore, evidence was provided that the reusable pen used in the clinical studies was similar to the combination product intended to be commercialised in terms of dose accuracy.

For the pen assembly process, an appropriate control strategy has been established including control of the incoming pen components, in-process controls and a set of parameters for release testing.

Appropriate extraction studies were performed with the cartridge components by using different extraction solvents and a panel of different analytical methods for volatile, semi-volatile and non-volatile extractables. Leachables were studied in ongoing stability studies. No leachable of toxicological or quality concern was detected so far.

Integrity of the cartridge, resealability of the stopper, and the effectiveness of antimicrobial preservation was also studied. The results presented sufficiently confirm that finished product sterility is maintained during shelf life prior to opening and under in-use conditions.

Finally, the compatibility of MK-1293 finished product formulation with the materials of the equipment used in the commercial manufacture was adequately studied.

Manufacture of the product and process controls

MK-1293 finished product is released for the EU at N.V. Organon, Oss, The Netherlands.

The target size of one MK-1293 finished product batch to be filled into cartridges has been specified. Combination product batch size is variable but will not be larger than the batch size of the incoming finished product in terms of cartridge units.

The manufacturing process of MK-1293 finished product starts with dissolving active substance in an initial quantity of water for injections and hydrochloride acid. After complete dissolution, the pH is adjusted to the target pH of 4.0. The target excipient quantities are calculated and added. The formulated bulk solution is filtered into a steam-sterilised holding tank. Then the bulk solution is sterile-filtered into a distribution manifold. The components of the container closure system are sterilised by sterilisation procedures compliant with Ph. Eur. requirements. Aseptic filling consists of initial insertion of the sterile plunger stopper into the depyrogenated cartridge, final insertion of plunger stopper, initial fill, final fill to target fill volume, and sterile combi-seal placement and sealing. Final container cartridges are 100% inspected.

Maximum process times have been established for each single process step within the drug product manufacturing process. Specification limits of the in-process controls and operational ranges of the process parameters are in compliance with the values evaluated during process development.

A Post Approval Change Management Protocol (PACMP) was included in the application covering a change in the pen assembly line. The activities proposed in support of the change are appropriate and comprehensive to evaluate a potential impact of the changed process on the finished product, to validate the new process and to ensure constant and unchanged product quality.

Process validation was confirmed by the production of three consecutive MK-1293 cartridge batches. The values of the critical process parameters and attributes of the formulation, sterilisation and filling steps as well as of IPCs were within the established ranges or met their acceptance criteria. The pen assembly process was validated by the manufacture of three distinct final assembly batches. Considering all data of the IPCs, the results of the visual inspection and the release data, the process was confirmed to be under control and capable to consistently produce MK-1293 combination product of intended quality.

The filter membranes used for finished product bulk filtration were validated.

Finally, shipping studies were performed in order to validate the transport of the filled cartridges and the assembled pens.

Product specification

The finished product specification includes physicochemical parameters of MK-1293, pharmaceutical properties and quality attributes of the combination product. The list of parameters is considered adequate for product control at release. Furthermore, a reduced shelf life specification is presented containing only stability-indicating parameters.

All analytical in-house methods are sufficiently described.

Validation data in line with ICH Q2 has been presented. Dose accuracy determination method according to DIN EN ISO 11608-1 was also validated for MK-1293 combination product control.

Batch release data of commercial batches of MK-1293 cartridges and MK-1293 combination products have been presented. All parameters fulfil the acceptance criteria.

The acceptance criteria established in the finished product specification are considered appropriately justified and approvable.

Stability of the product

The stability data fulfil the acceptance criteria of all parameters at the recommended storage conditions (5±3°C). Based on 24 months stability data presented for three finished product cartridge batches, a finished product shelf-life of 24 months at 5°C is approvable.

In-use stability was investigated with stored cartridges at the 12-, 18- and 24-month time point of the formal stability study after assembling the cartridges with the pen. The claimed shelf life of 28 days for MK-1293 combination product after first opening is supported. The storage instructions given in the SPC and in the user instructions comply with the conditions tested and are found to be appropriate.

Additional stability studies were conducted to support the proposed range for temperature during shipping and to confirm light protection when the MK-1293 cartridge is located in the pen and with a closed cap.

Adventitious agents

Only one animal derived material is used in the manufacturing process of MK-1293. This material can be considered to comply with EMEA/410/01 as it is derived from bovine milk sourced from healthy animals and fit for human consumption. No other ruminant materials are used in the preparation. The TSE safety is therefore considered adequate.

Biosimilarity

An analytical similarity exercise was conducted to compare the test product MK-1293 with the reference product Lantus, approved in the EU. In addition, analytical bridging was performed to compare the proposed biosimilar, EU Lantus reference product and US Lantus comparator.

Results from the analytical similarity study were evaluated using a combination of numerical/statistical and analytical assessments in a three-tiered approach. The approach was in general considered appropriate.

Multiple MK-1293 finished product batches containing active substance manufactured by the commercial process as well as multiple EU Lantus and US Lantus batches were included in the similarity assessment.

The choice of the test and reference product was appropriate, taking into consideration the quantity, representativeness and differences in age. Test and reference products were tested at two different analytical laboratories, where two tests were significantly different. For all other analytical methods it was confirmed that the same analytical methods were used at both testing sites. It was clarified that the results of the analytical similarity testing were obtained from side-by-side testing of the test and the reference products with the exception that for the comparative stability study testing occurred at same laboratory within 28 days of receipt of samples, but not necessarily side-by-side.

The structural comparability of MK-1293 versus EU Lantus and US Lantus was studied by applying numerous analytical state-of-the-art methods.

Comparable biological activity against the insulin receptor and the Insulin-like Growth Factor-1 was demonstrated for the proposed biosimilar, the EU Lantus reference product and the US Lantus comparator.

Analysis of data for potency/assay, protein content and aggregates by HP-SEC as well as related proteins as total impurities and largest single impurity by RP-UPLC showed that the proposed biosimilar falls within the quantitative margins for the EU/US Lantus reference products. However, differences in the impurity profiles of the test and the reference product became evident when tested by RP-UPLC. The primary product-related impurities of the proposed biosimilar are not present in Lantus. However, levels in the biosimilar are low, and detectable by UPLC only. Based on the fact that the overall level of UPLC impurities is lower in the proposed biosimilar it was concluded that the proposed biosimilar is comparable to the EU reference product and the US comparator. Results from in silico studies indicated that these impurities have low potential for immunogenicity.

For the osmolality attribute, a difference between the test substance and EU/US Lantus was noted. This was expected since there is a difference in glycerol concentration in the formulations. However, the osmolality of the proposed biosimilar is within an acceptable range and there is no impact on product quality or stability.

Comparative stability studies were performed with the proposed biosimilar, the reference product EU Lantus and the comparator US Lantus. For almost all of the comparisons, there was no difference between MK-1293, EU and US Lantus. For aggregates, charge variants, m-cresol and zinc contents and osmolality statistical analysis revealed small differences in the trends which all were concluded to be not relevant based on a scientific justification. This stability data support the comparability between the proposed biosimilar and the reference product EU Lantus as well as the bridging between EU and US Lantus.

As part of the analytical similarity exercise, forced degradation studies were performed with the proposed biosimilar and EU/US Lantus. Formation of aggregates, hydrophobic species and acidic variants were the main degradation pathways. Equivalent or even lower degradation rates as well as lower level of impurities could be demonstrated for the proposed biosimilar compared to EU Lantus. In addition, EU Lantus showed comparable rates of degradation when compared with US Lantus.

Summarising, a sufficiently high number of MK-1293 finished product batches manufactured by the commercial process as well as of the Lantus reference product authorised in the EU was included in the analytical similarity exercise. As US Lantus has been used for pre-clinical and clinical studies investigation of US Lantus batches were also included in the analytical similarity exercise to support bridging between the US comparator and the EU reference product.

Based on the analytical comparability exercise similarity between MK-1293 and the reference product EU Lantus is considered demonstrated on quality level. In addition and based on analytical bridging data the comparator US Lantus is considered representative of the EU reference product EU Lantus.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

Four post approval change management protocols (PACMP) have been in included in the dossier and are considered acceptable. Two PACMPs relate to the qualification, manufacture and release of a new WCB. One PACMP is included to implement an intended future commercial process for the active substance. One PACMP is for the introduction of changes in the pen assembly line.

Lusduna has been developed as a biosimilar to the EU reference product Lantus. Overall, similarity between Lusduna and the reference product EU Lantus is considered demonstrated at the quality level. Minor differences in impurity profile and osmolality have been justified. In addition, based on analytical bridging data, the comparator product US Lantus is considered representative of the reference product EU Lantus.

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. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Pharmacology

As requested for a biosimilar application, the Applicant performed in-vitro comparison of their product MK-1293 with the reference product Lantus at three levels, receptor binding, receptor activation (autophosphorylation) and metabolic function (glucose uptake and others). This comparability exercise was done in first experiments with Lantus sourced from USA and, in consecutive studies, with Lantus sourced from EU to fulfil the requirements of the CHMP biosimilarity guideline. The applicant has provided analytical data that demonstrated that Lantus sourced from the US was representative for Lantus sourced from the EU in the studies performed in this application. Also, the MK-1293 material used in the earlier studies is considered comparable to the final material. Hence, results from the earlier studies using US-Lantus are relevant for the biosimilarity exercise. The methods used for US- and EU-Lantus were in part different. Beside binding to the cognate insulin receptor (IR) and testing metabolic action, the Applicant also studies binding to the off-target IGF-1 receptor (IFG1R) and determined mitogenic activity.

The nonclinical pharmacologic programme supporting development of MK-1293 included comparison of:

- Binding of MK-1293 and Lantus to insulin receptor (IR)
- Activation of IR by MK-1293 and Lantus
- Functional assays of IR activation by MK-1293 and Lantus
- Binding of MK-1293 and Lantus to insulin-like growth factor 1 receptor (IGF1R)
- Activation of IGF1R by MK-1293 and Lantus
- Mitogenic potential of MK-1293 and Lantus
- Efficacy of MK-1293 and Lantus in rat and dog models of human T1DM

The following table provides an overview of the PD studies conducted.

Table 4: List of Nonclinical Pharmacologic Studies Supporting Development of MK-1293

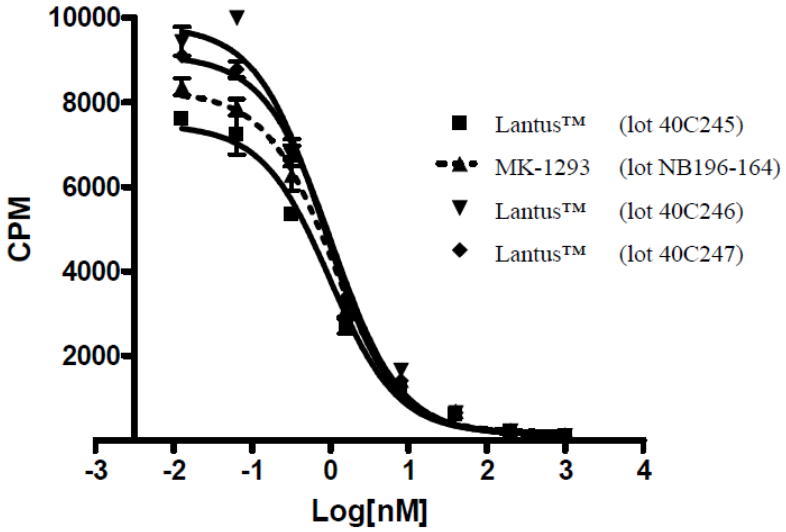
Report no.	Study title	Species	Testing facility	GLP
in vitro				
PD001	In Vitro Characterization of MK-1293 [US-Lantus used]	In vitro	MRL, Kenilworth, NJ	No
PD004	Comparison of Binding of MK-1293 and EU-approved Lantus to Isoforms A and B of Insulin Receptor and Insulin- like Growth Factor 1 Receptor	In vitro	MRL, Kenilworth, NJ	No
PD005	Comparison of Activation of Isoform A of Insulin Receptor by MK-1293 and EU-approved Lantus	In vitro	MRL, Kenilworth, NJ	No
PD006	Comparison of Effects of MK-1293 and EU-approved Lantus on Induction of Insulin Receptor-dependent Glucose Uptake	In vitro	MRL, Kenilworth, NJ	No
PD007	Comparison of Effects of MK-1293 and EU-approved Lantus on Mitogenesis	In vitro	MRL, Kenilworth, NJ	No
PD008	Comparison of Inhibition of Insulin Receptor-dependent Lipolysis by MK-1293 and EU-approved Lantus	In vitro	MRL, Kenilworth, NJ	No
PD009	Comparison of Inhibition of Glucose Production by MK-1293 and EU-approved Lantus	In vitro	MRL, Kenilworth, NJ	No
PD010	Comparison of Activation of Isoform B of insulin receptor by MK-1293 and EU-approved Lantus	In vitro	MRL, Kenilworth, NJ	No
in vivo				
PD002	In Vivo Characterization of MK-1293 in Streptozotocin-Rats [US-Lantus used]	Rat	MRL, Kenilworth, NJ	No
PD003	In Vivo Characterization of MK-1293 in Somatostatin-treated Dogs [US-Lantus used]	Dog	MRL, Kenilworth, NJ	No

In vitro studies

Insulin receptor (IR) binding

Done within study PD001

Binding of MK-1293 and **US-Lantus** to IR was assessed by a competition-inhibition assay in Chinese hamster ovary cells expressing recombinant human IR-B, i.e. the long isoform of the human insulin receptor which is thought to be mainly involved in metabolic processes. The obtained binding curves, showing dose-dependent competition of tracer binding, are depicted in the figure below. When quantified as IC50s, MK-1293 and Lantus lots 40C245 and 40C247 bound to IR with slightly lower potency (higher IC50 values) compared to Lantus lot 40C246. When expressed as relative potencies, MK-1293 and Lantus lots 40C245 and 40C247 bound to IR with a similar potency; no statistically significant differences were observed.



Binding of MK-1293 and Lantus to IR-B. Experiment ("run") 1 out of three is shown; data points represent samples in triplicate.

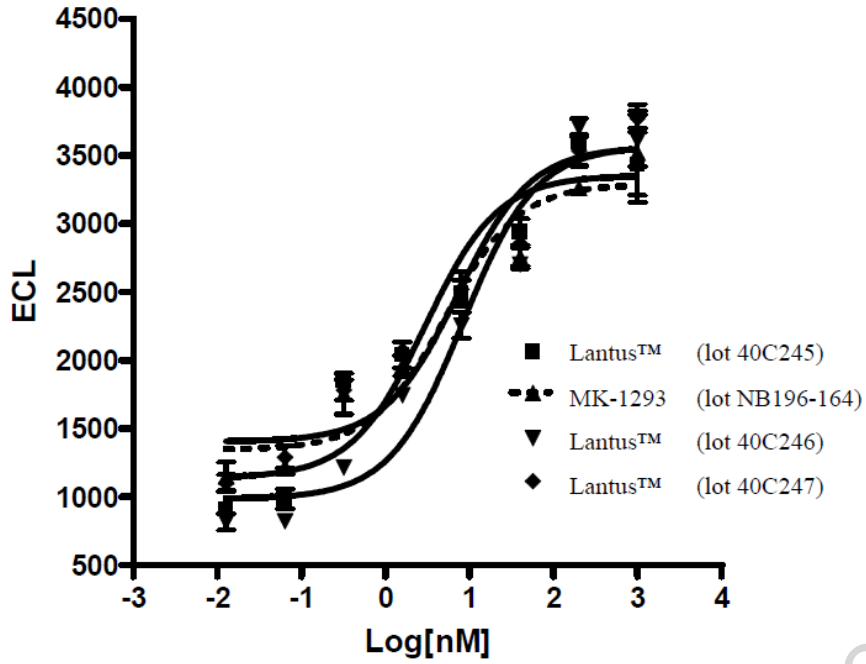
This classical receptor binding experiment shows that the displacement curve of MK-1293 is situated well within the range of various lots of Lantus and thereby demonstrates biosimilarity at the receptor binding level. The quality of the experiment is good, identified by the small error bars and the good fit of the sigmoid curve. The comparator was Lantus sourced in the US; pharmaceutical bridging data provided by the applicant did show that US-Lantus is representative for EU-Lantus.

IR activation (IR phosphorylation)

Done within study PD001

Activation of IR by MK-1293 and **US-Lantus** was measured by tyrosine phosphorylation of IR in the human hepatocellular carcinoma cell line HepG2 endogenously expressing IR. RT-PCR experiments revealed that the HepG2 cells used express both IR subtypes, IR-A and IR-B, in line with literature reports.

A representative result is shown in the figure below. This figure shows experiment ("run") 1 out of three. The other two experiments yielded similar results. When quantified as EC50s, MK-1293 and Lantus activated IR with a similar potency. When expressed as relative potencies, activation of IR by MK-1293 and Lantus was also similar; no statistically significant differences were observed.



Activation of IR by MK-1293 and Lantus. Experiment ("run") 1 out of three is shown; data points represent samples in triplicate.

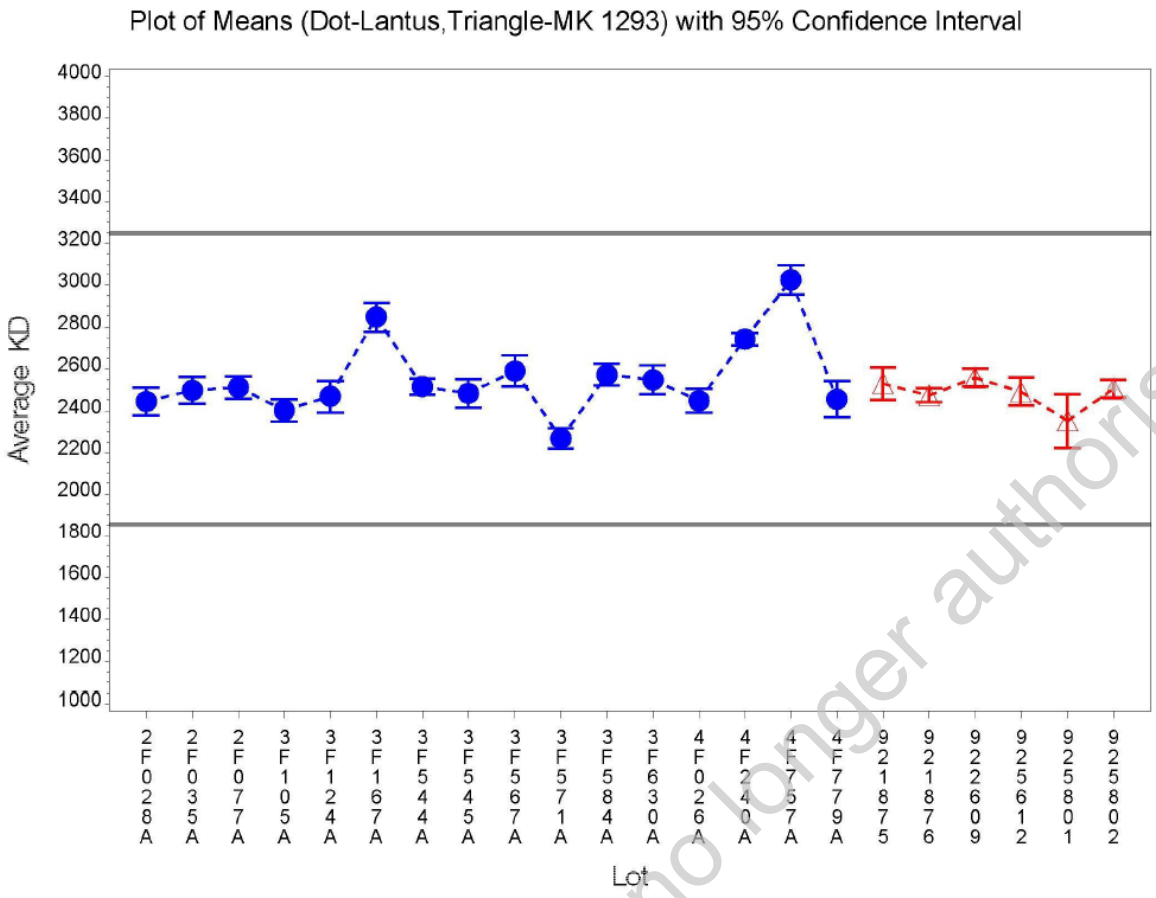
The effect size, i.e. the difference between the receptor activities at the low vs. the high concentrations, was somewhat smaller with MK-1293 than with any batch of Lantus according to the fitted curves. However, the curve fit was no so good here as with receptor binding. For unknown reasons the data points are not well aligned along a sigmoid curve. Hence, the fitted curves appear somewhat arbitrary. On the other hand, the data points of MK-1293 and Lantus lie close together. Hence, it can be concluded that MK-1293 and (US-)Lantus behave similar in respect to receptor activation.

Binding to the two IR isoforms (IR-A and IR-B)

Study PD004

Binding of MK-1293 in direct comparison with **EU Lantus** to the two insulin receptor isoforms (splicing variants) IR-A and IR-B was measured by the Biacore method. IR-B is considered the "normal" insulin receptor, being mainly responsible for the metabolic effects whereas the shorter form IR-A may be involved in mediating proliferative insulin effects. The recombinant soluble receptor protein fragments of IR-A and IR-B used in this Biacore-based assay were purchased from R&D Systems, Minneapolis, MN, USA.

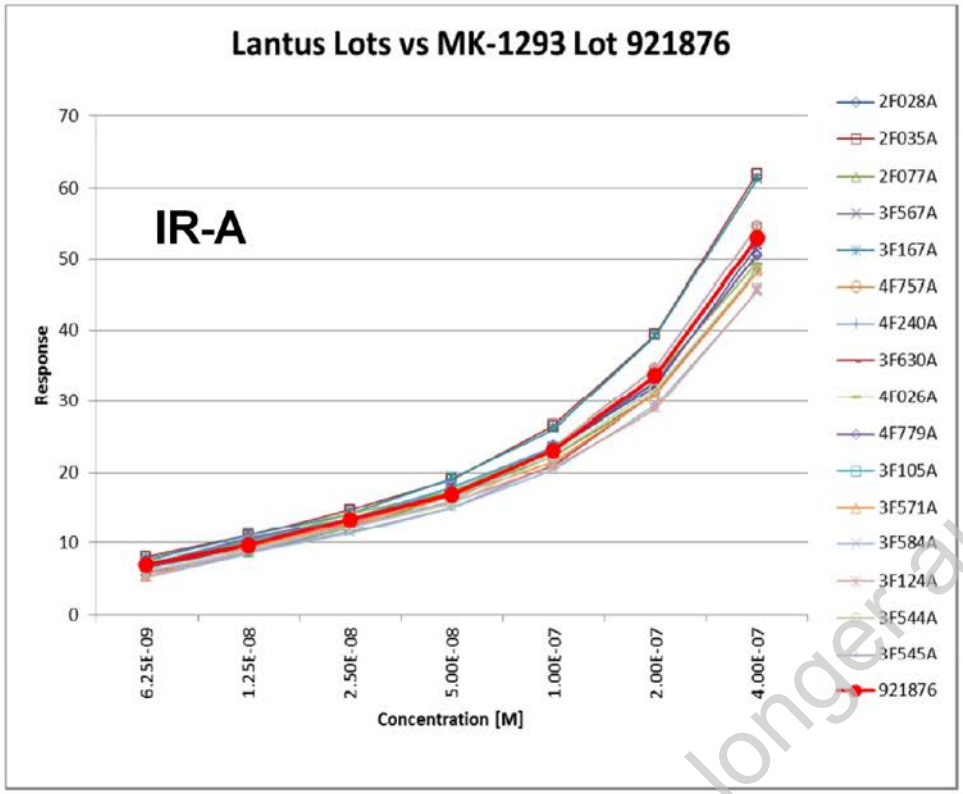
The mean K_D values for binding of MK-1293 to **IR-B** ranged from 2351 to 2557 nM and for binding of Lantus to IR-B from 2268 to 3024 nM (see figure below). The mean relative affinities for binding of MK-1293 to IR-B ranged from 91 % to 119% and for binding of Lantus to IR-B from 77% to 124%.

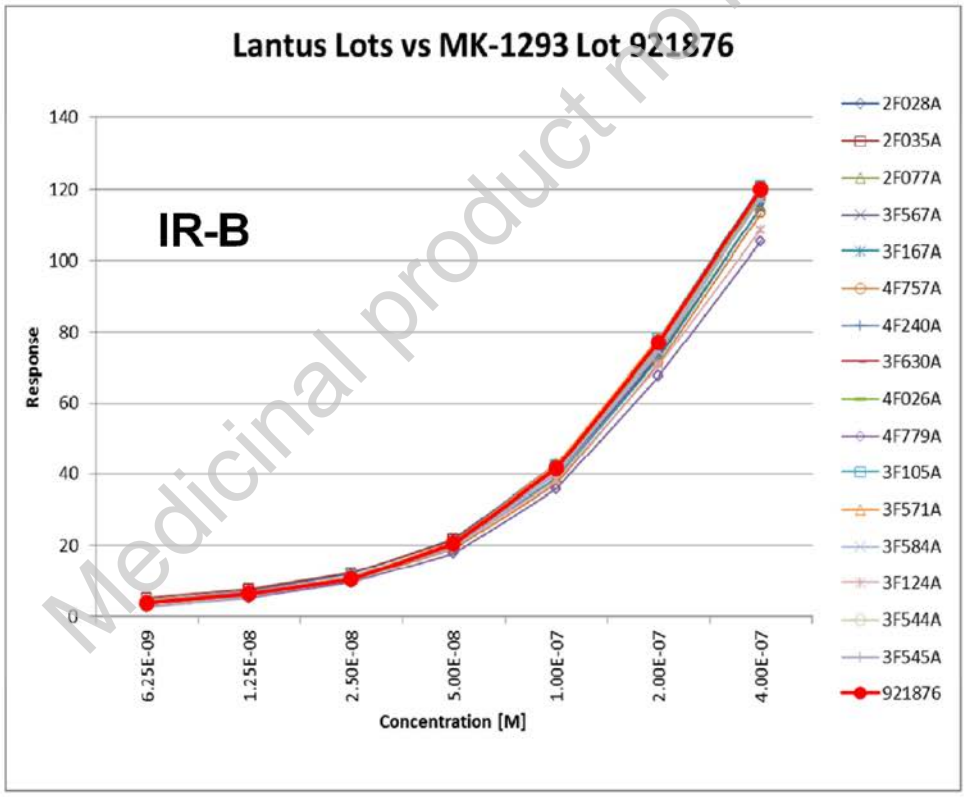


Binding of MK-1293 and Lantus to IR-B. Values are presented as mean of at least 6 individual determinations. Error bars represent the 95% confidence interval. The grey lines in the graph represent tolerance interval. Values for Lantus are represented by blue dots, and values for MK-1293 are represented by red triangles.

In contrast to Study PD001 the Applicant has not used the classical receptor binding assay here but a Biacore-based method for determining binding of MK-1293 compared to EU-Lantus. For the Biacore method it is necessary to use a soluble fragment of the receptor instead of the native receptor. Hence, the system is somewhat artificial. Nevertheless, for the actual purpose, comparison of a biosimilar product with the comparator, the approach appears appropriate.

The Applicant also provided the binding curves from which the above mentioned K_D values were calculated (see figure below). It turned out that the concentration range selected did not cover the complete response range; i.e. the glargine concentrations were far too low for approaching maximal binding. Sigmoid curves are expected; the presented graphs obviously represent the ascending part of a sigmoid curve. K_D values usually indicate the concentration where half-maximal binding is achieved so that they are difficult to calculate when maximal binding cannot be estimated. Thus, the values provided by the Applicant are not very reliable. Nevertheless, the biosimilarity exercise does not depend on the calculation of K_D values. Shape, position and quality of fit of the binding curve provide much more information about similarity than a single K_D value. In this respect, the provided curves (one representative MSD batch out six is shown in the figure below) convincingly demonstrate that the tested MSD batches behave like the tested Lantus batches. The number of data points is sufficient for reliable conclusions.





Binding of insulin glargine to IR-A and IR-B in the Biacore assay

The Biacore readout ("Response") is displayed on the y-axis in arbitrary units. Glargine concentrations are plotted on the x-axis in logarithmic scale. One representative batch (out of six) of MK-1293 is shown along with 16 Lantus batches as indicated.

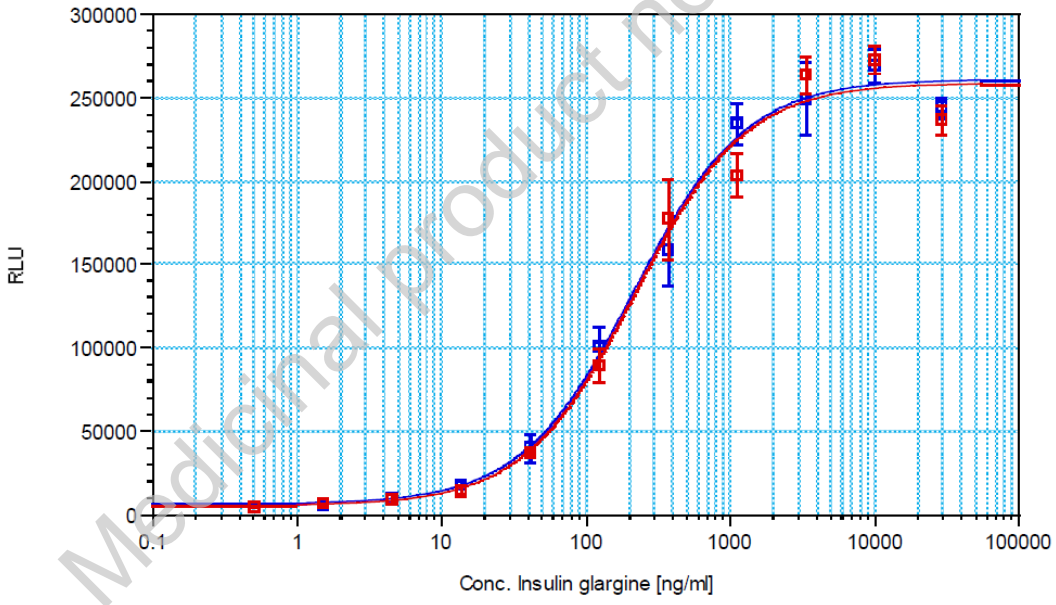
It should also be noted that a K_D of 2500 nM for binding of insulin to its receptor is very high; it usually lies in the low nanomolar range. However, it is acknowledged that the artificial, soluble receptor fragment used for this Biacore assay may display a markedly lower affinity for insulin than the native receptor. The absolute K_D value is not relevant for demonstrating biosimilarity; it is important that the binding curves are highly similar for test vs. reference compound.

IR-A activation

Study PD005

Activation of isoform A of insulin receptor (IR-A) by MK-1293 and **EU-Lantus** was assessed in an IR tyrosine phosphorylation assay using Chinese hamster ovary cells expressing human IR-A (IRA/CHO-K1). Phosphorylation of IR-A is a measure of its activation. The levels of phosphorylated receptor protein were measured in cell lysates using the Insulin Signaling Panel (Phospho Protein) Whole Cell Lysate Kit sold by Meso Scale Diagnostics (MSD), Rockville, Maryland, USA. This assay is based on the ELISA principle; the plate contains electrodes, and the label of the secondary antibody emits light when voltage is applied

The mean relative potency of MK-1293 for activation of IR-A ranged from 90% to 100%. The mean relative potency of Lantus for activation of IR-A ranged from 84% to 111%. The results of a representative run are presented in the figure below.



□ MK-1293, lot 925612 □ Lantus™, lot 2F043A

Activation of IR-A by MK-1293 and Lantus. Dose-response curves from a representative run are shown.

Detection of phosphorylated insulin receptor (splicing variant IR-A) was done by a commercial, ELISA-like assay and not by the classical way, i.e. Western blotting. Thus, there is less information on this assay in the literature. Nevertheless it confirms the validity of this assay that the data points neatly fit to the expected sigmoid

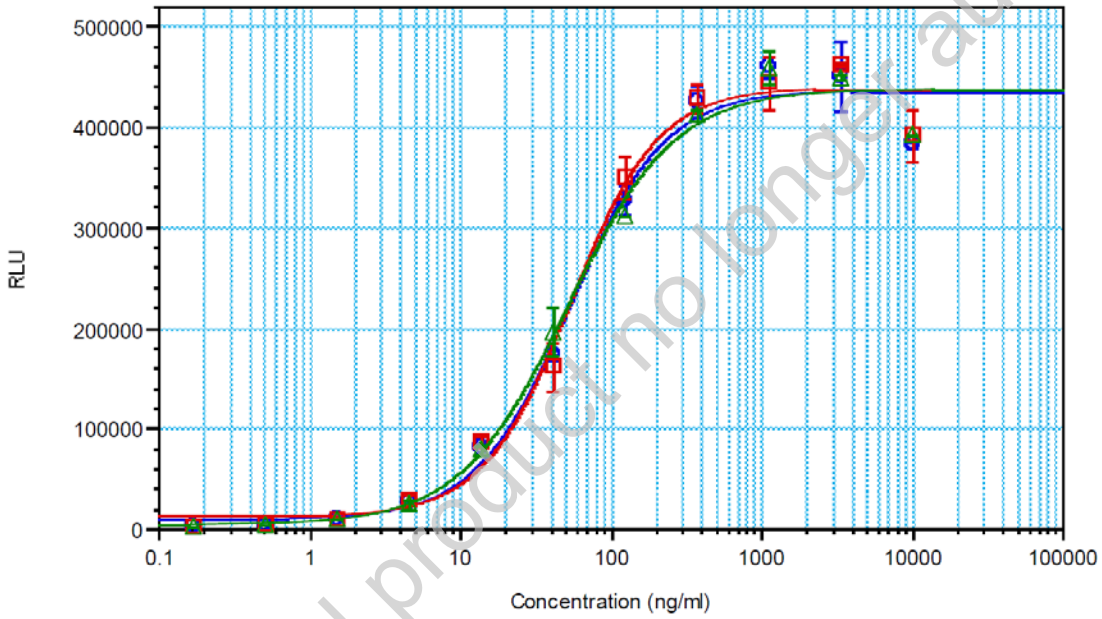
concentration-response curve. In the curves shown, the half-maximal effect was reached with around 200 ng/ml of glargine. With a molecular mass of around 6 kDa, 200 ng/ml correspond to 33 nM. This is a realistic value for in-vitro experiments.

IR-B activation

Study PD010

Methods were the same as used in Study PD005 on IR-A and are described above.

The mean relative potency of MK-1293 for activation of IR-B ranged from 93% to 113%. The mean relative potency of Lantus for activation of IR-B ranged from 95% to 119%. The results of a representative experiment are presented in the figure below.



○MK-1293 Reference, lot 925612; □ MK-1293, lot 921875; Δ Lantus, lot 2F028A

Activation of IR-B by MK-1293 and Lantus. Dose-response curves from a representative experiment are shown.

The shape of the curves confirms the validity of this assay that the data points neatly fit to the expected sigmoid concentration-response curve. In the curves shown, the half-maximal effect was reached with around 50 ng/ml of glargine. With a molecular mass of around 6 kDa, 50 ng/ml correspond to 8 nM. This is a realistic value for in-vitro experiments.

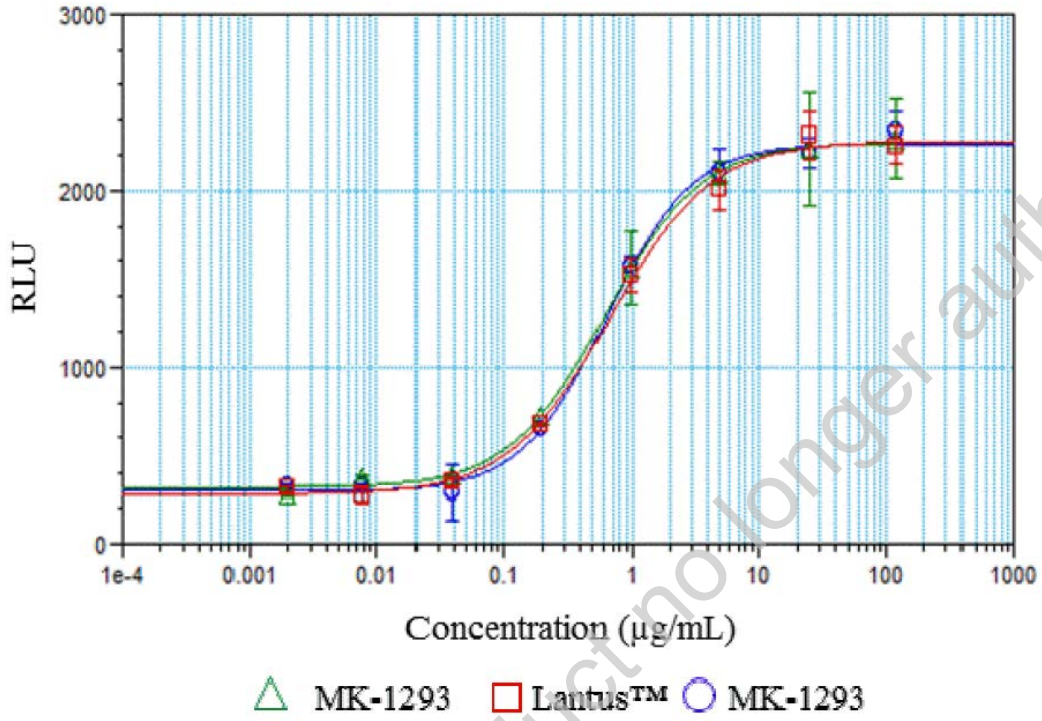
Glucose uptake

Study PD006

Induction of insulin receptor (IR)-dependent glucose uptake was assessed in mouse 3T3-L1 cells differentiated into adipocytes. Glucose uptake was followed using 2-deoxy-D-glucose (2DG) labelled with ^{14}C (^{14}C-2DG). For comparison, glucose uptake in response to human insulin (Humulin R) and to IGF1 was also tested.

The mean potency values for induction of IR-dependent glucose uptake by MK-1293 ranged from 89% to 107%. The mean potency values for induction of IR-dependent glucose uptake by Lantus ranged from 84% to 105%.

The results of a representative experiment ("run") are presented in the figure below.



Induction of IR-dependent Glucose Uptake by MK-1293 and Lantus. The dose-response curves from a representative run are shown. Data are given as means +/- standard deviations. In this representative graph, MK-1293, lot 925612 was compared to itself and to Lantus, lot 4F240A. RLU = relative light unit.

The data points of this glucose uptake assay reveal little variability. Furthermore, a sigmoid concentration-response curve can easily be fitted, arguing for the reliability of the data. The half-maximal effect was reached at about 0.5 µg/ml of glargine, corresponding to around 80 nM. Although in vivo lower insulin concentrations are already active, this value meets the expectations for in vitro experiments. The results of this glucose assay were very accurate what is unusual for a whole-cell assay. In order to demonstrate that the assay also can detect differences between different test substances, the Applicant also tested human insulin and IGF-1 in this test system. As desired, the resulting curves were markedly different from the glargine curve.

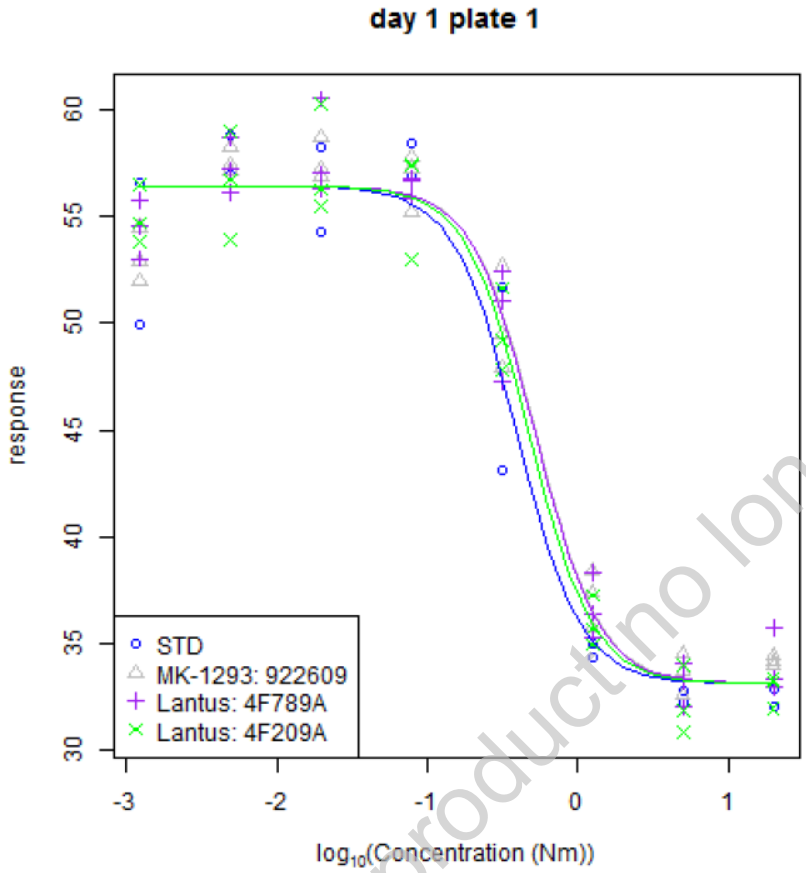
Inhibition of lipolysis

Study PD008

The study was performed with primary mouse adipocytes, isolated from the epididymal fat pads of male C57Bl/6 mice (Taconic Biosciences). Mice were 7-8 weeks old at time of adipocyte collection and had been fed regular rodent chow. The primary cells were incubated with descending concentrations, 0.005 nM - 20 nM in 1:4 serial dilutions, of insulin glargine (MK-1293 or Lantus) for 1.5 hours. Thereafter, incubation medium was removed and its glycerol content was determined. Glycerol released from the cells is a marker for lipolysis.

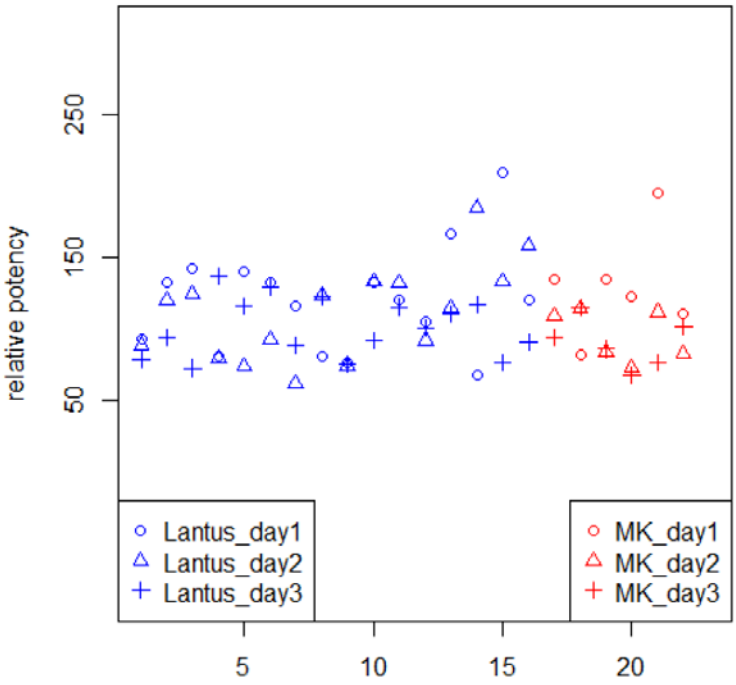
Several batches of Lantus and MK1293 were tested (6 for MK-1293 and 16 for Lantus). With each batch three experiments were performed on three different days.

A representative concentration-response curve is shown below. It reveals that data points could be well fitted, indicating that the experiments were well performed and the calculated potency values are reliable. The variability is higher than with the binding assays described above, but this is most likely due to the more complex test system.



Plot of the raw concentration-response data
Results for the MK-1293 standard, one MK-1293 sample (batch 922609) and two different Lantus batches are shown as indicated, along with the fitted curves.

The Applicant analysed the raw data by calculating the relative potency with MK-1293 lot 925612 as reference. The shape of the curves shown above and the quality of fit indicate that the calculated potency values are reliable and can serve for demonstrating similarity between MK-1293 and Lantus. The relative potency for each batch tested (Lantus or MK-1293) and for each replicate experiment (labelled as "_day 1" to "_day 3") are plotted in the following figure. No relevant differences between MK-1293 and Lantus became obvious.



Plot of individual relative potency values (expressed as percent)
Potency for each MK-1293 (red) and Lantus (blue) batch was derived from the concentration-response curves by fitting a sigmoid curve. Potency was normalised to a MK-1293 standard to yield the %relative potency values shown in the figure.

Taken together, MK-1293 and Lantus behaved similar in the inhibition of lipolysis experiments.

Inhibition of glucose production

Study PD009

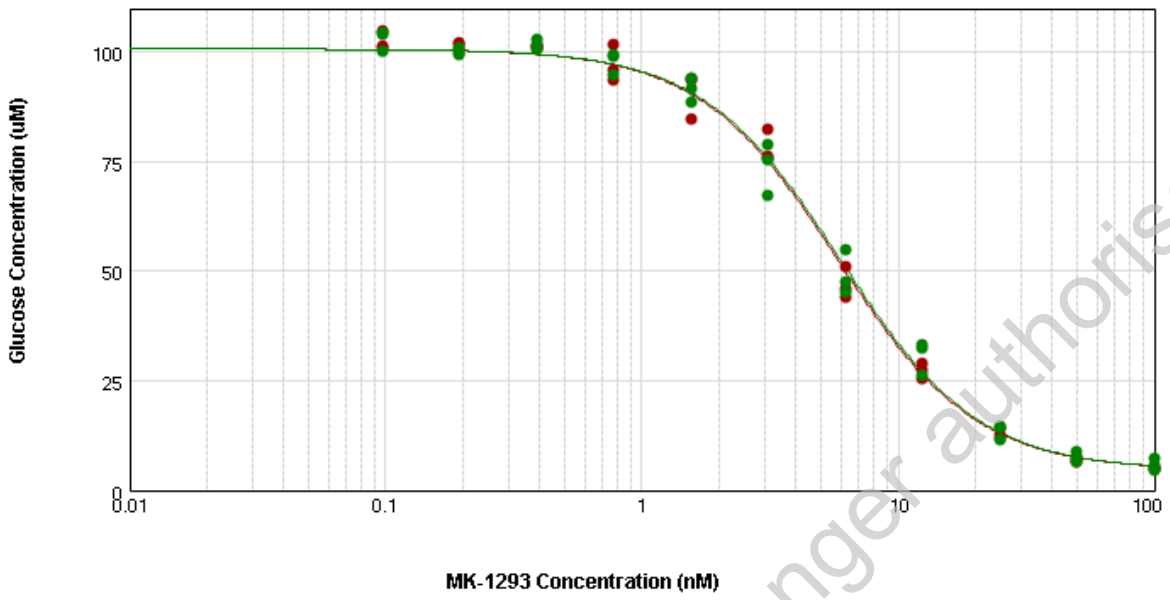
Glucose production and its inhibition by glargine was measured in rat H-4-II-E hepatoma cells. Six batches of MK-1293 and 16 batches of Lantus were employed.

The H-4-II-E liver cells were cultured for 2-3 days prior to assay initiation. To set up the assay, the H-4-II-E cells were plated in H-4-II-E growth medium and allowed to adhere to the 96-well plate overnight. On Day 1, the cells were starved of serum and allowed to incubate overnight. On Day 2, the cells were starved of serum and glucose for 3-7 hours followed by treatment with serial dilutions of MK-1293 reference sample, MK-1293 test lots, or Lantus for 72 hours. The supernatant was collected from the standard and sample treated wells and glucose concentration was determined using the Amplex Red Glucose Assay kit (Life Technologies). This kit utilises an enzymatic glucose oxidation reaction which in several steps converts a special dye to a fluorescent product which can be measured optically. Samples were tested on triplicate plates.

From the descending concentrations of glargine, concentration-response curves were fitted. From these, potency (a parameter similar to EC50) was calculated. An MK-1293 standard was defined, and potency of each sample was related to this standard, giving rise to the relative potency (rp) values which were used for comparing the different batches of MK-1293 and Lantus. In order to estimate the sensitivity of the assay for detecting differences, IGF1 was also tested as an alternative IR ligand.

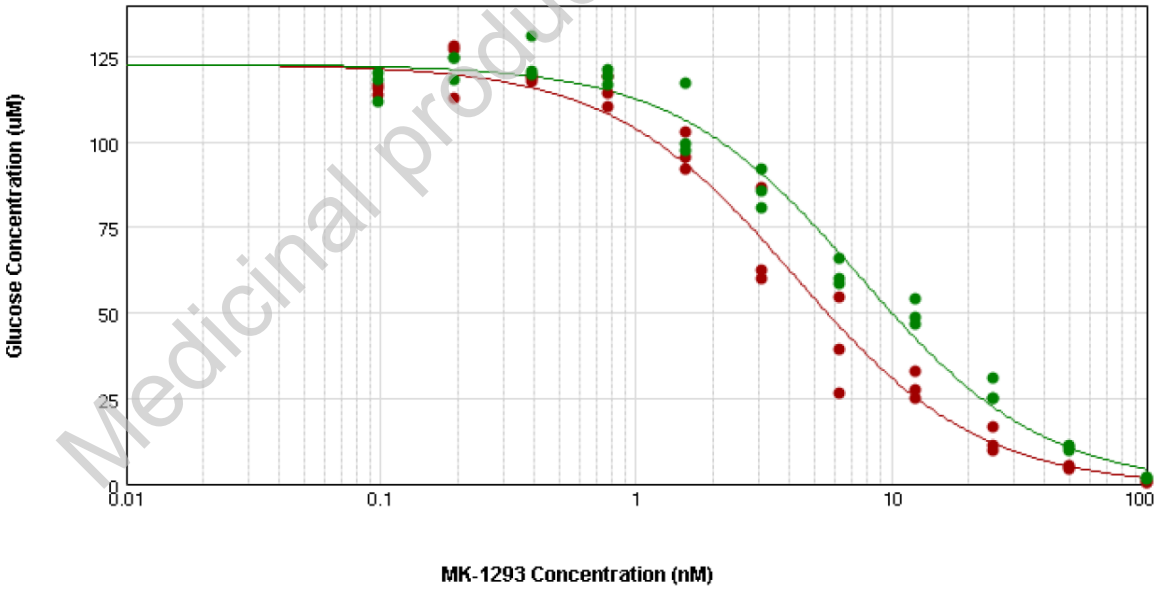
Reliable calculation of EC50 or potency requires a plausible and sigmoid shape of the concentration-response curve and requires that the glargine concentrations tested cover the whole range of the response from none to

maximal. These conditions were fulfilled as can be seen in an exemplary experiment (MK-1293 standard and Lantus Lot 4F209A) shown in the figure below.



Dose Response Curve of MK-1293 Standard and Lantus Sample
Decreasing glucose production (measured as glucose concentration in the cell culture medium) in response to increasing glargine concentration is show. Red symbols and fitting curve are MK-1293 standard; green symbols and line are Lantus Batch 4F209A.

Using IGF1 instead of insulinn glargine yielded a clearly different response curve as shown below.



Dose Response Curve of MK-1293 Standard and IGF-1 Control Sample
Decreasing glucose production (measured as glucose concentration in the cell culture medium) in response to increasing MK-1293 or IGF1 concentration is show. Red symbols and fitting curve are MK-1293 standard; green symbols and line are IGF1.

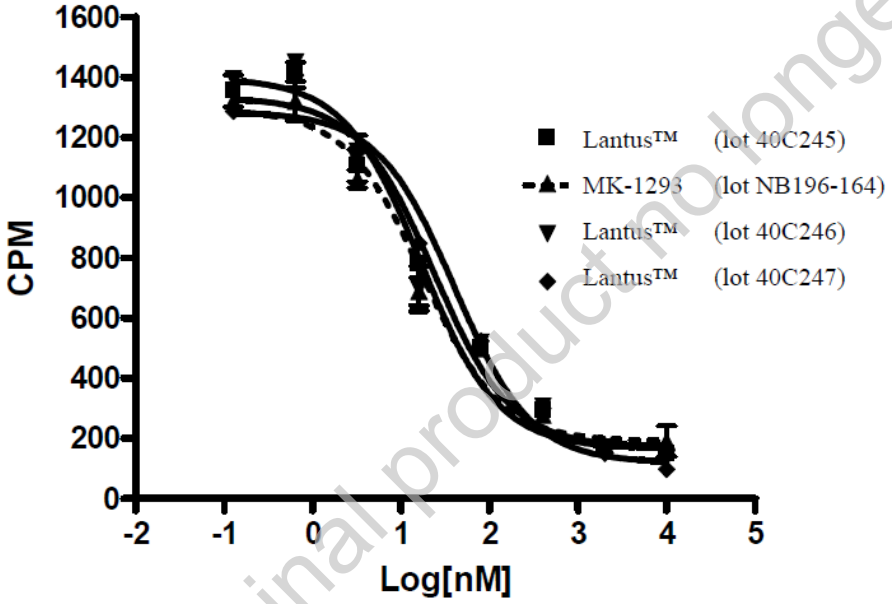
The mean relative potency of MK-1293 for inhibition of insulin receptor-dependent glucose production ranged from 92.3% to 110.18% . The mean relative potency of Lantus™ for inhibition of insulin receptor-dependent glucose production ranged from 95.59% to 120.51%. Thus, MK-1293 and Lantus can be considered similar in this assay.

IGF1 receptor (IGF1R) binding

Data from study PD001 for US-Lantus

Binding of MK-1293 and **US-Lantus** to insulin-like growth factor 1 receptor (IGF1R) was assessed in a competition-inhibition assay. Assays were conducted in CHO cells expressing recombinant human IGF1R (CHO-IGF1R). Radiolabeled recombinant human IGF-1 (^{125}I-human IGF-1) was used as a tracer and unlabelled MK-1293 and Lantus were used as a competitor.

Binding of MK-1293 and Lantus to IGF1R is depicted in the figure below (Experiment["Run"]1); the results of Runs 2 and 3 were similar. When quantified as IC_{50}s, MK-1293 and Lantus bound to IGF1R with a similar potency of around 17 to 26 nM. There was one outlier with Lantus Batch 40C247 in Run 1, yielding 40.1 nM. When expressed as relative potencies, binding of MK-1293 and Lantus to IGF1R was also similar; the ratios (except one outlier) ranged from 0.75 to 1.66. No statistically significant differences were observed.

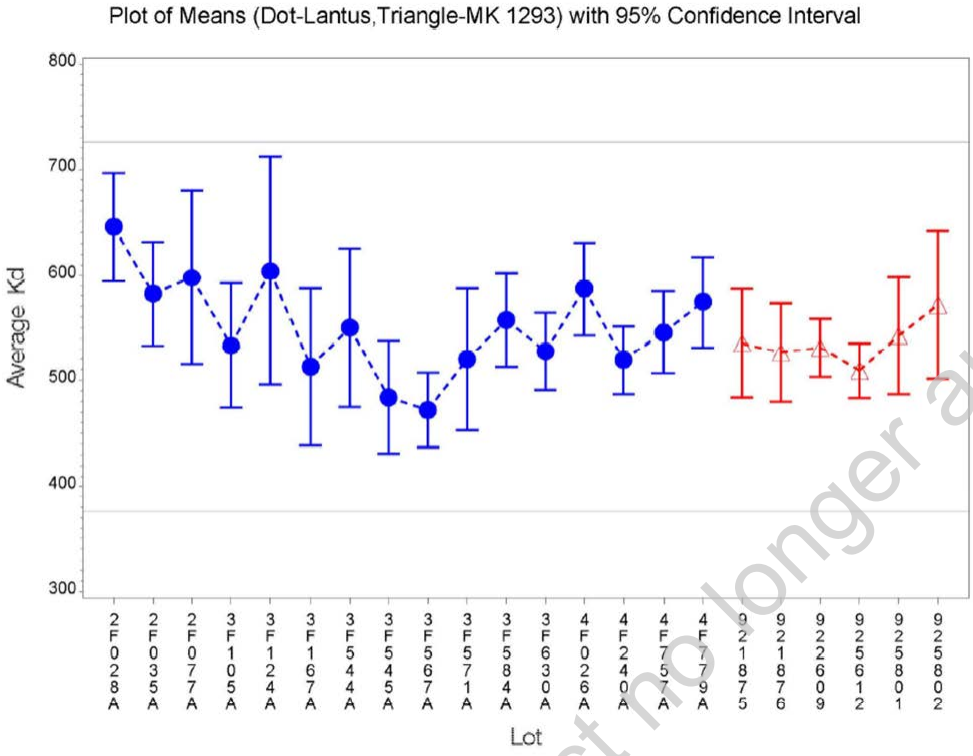


Binding of MK-1293 and Lantus to IGF1R: Run 1; CPM = counts per minute.

Data from study PD004 for EU-Lantus

Binding of MK-1293 in direct comparison with **EU Lantus** to the IGF-1 receptor (IGF1R) was also determined within this study. The recombinant soluble receptor protein fragments of IGF1R used in this Biacore-based assay were purchased from R&D Systems, Minneapolis, MN, USA. For more details see description of the IR-A and IR-B part of Study PD004 above.

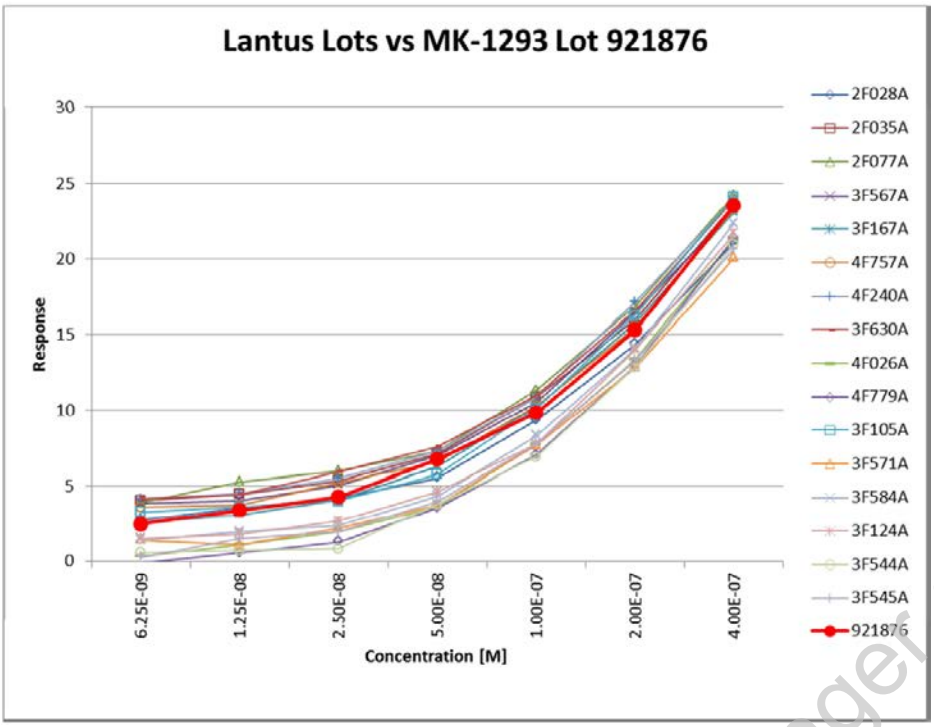
The mean K_D values for binding of MK-1293 to **IGF1R** ranged from 510 to 571 nM and for binding of Lantus to IGF1R from 472 to 645 nM (see figure below). The mean relative affinities for binding of MK-1293 to IGF1R ranged from 91% to 111% and for binding of Lantus to IGF1R from 75% to 117%.



Binding of MK-1293 and Lantus to IGF1R. Values are presented as mean of at least 6 individual determinations. Error bars represent the 95 % confidence interval. The grey lines in the graph represent tolerance interval. Values for Lantus are represented by blue dots, and values for MK-1293 are represented by red triangles.

As for IR-A and IR-B binding (see respective section above), the Applicant also provided the binding curves from which the K_D values were calculated; see following figure. As for IR-A and IR-B binding, it turned out that the concentration range selected did not cover the complete response range: Thus, the K_D values provided by the Applicant are not reliable and in fact are not plausible. The K_D values calculated by the Applicant for binding of glargine to the IGF1 receptor are in the same range as for binding to IR-A although it is known that binding of insulins to IGF1R is much weaker than to IRs.

Nevertheless, the biosimilarity exercise does not depend on the calculation of K_D values as discussed in the section on IR-A and IR-B binding. The provided curves (one representative MSD batch out six is shown in the figure below) demonstrate that the tested MSD batches behave like the tested Lantus batches. The number of data points is sufficient for reliable conclusions.



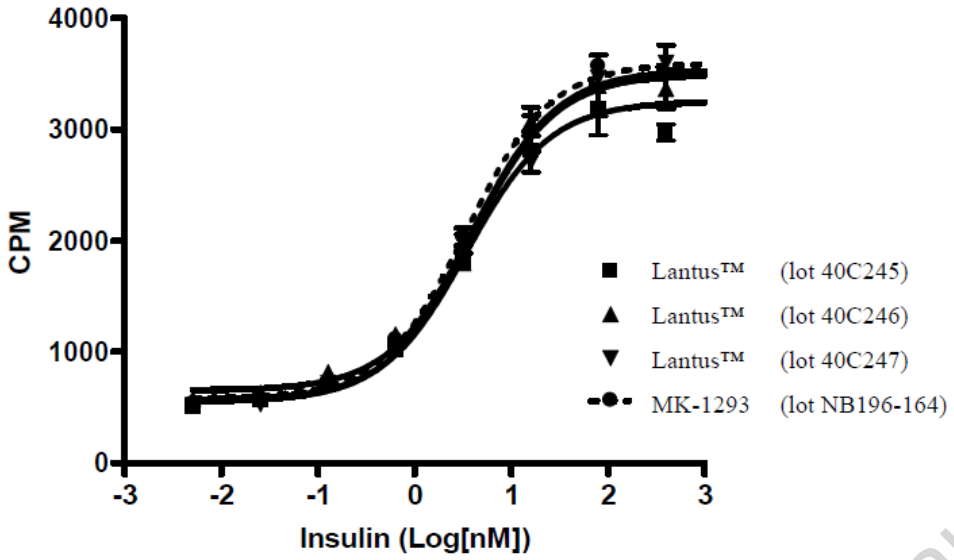
Binding of insulin glargine to IGF1R in the Biacore assay
The Biacore readout ("Response") is displayed on the y-axis in arbitrary units. Glargine concentrations are plotted on the x-axis in logarithmic scale. One representative batch (out of six) of MK-1293 is shown along with 16 Lantus batches as indicated.

Mitogenic potential

Mitogenic potential was assessed in two studies, one (PD001) using US-Lantus and the other (PD007) using EU-Lantus as comparator.

Data from Study PD001 (US-Lantus)

Mitogenic potential of MK-1293 and **US-Lantus** was analysed in a tritium-labelled thymidine uptake assay using Saos-2/B10 cells. The results are shown in the figure below (one representative experiment out of three). A high similarity between MK-1293 and US-Lantus was shown at the level of IGF1R binding. The variability of the data (indicated as SEM) was small, and the data points very well fitted a sigmoid curve, arguing for good data quality.

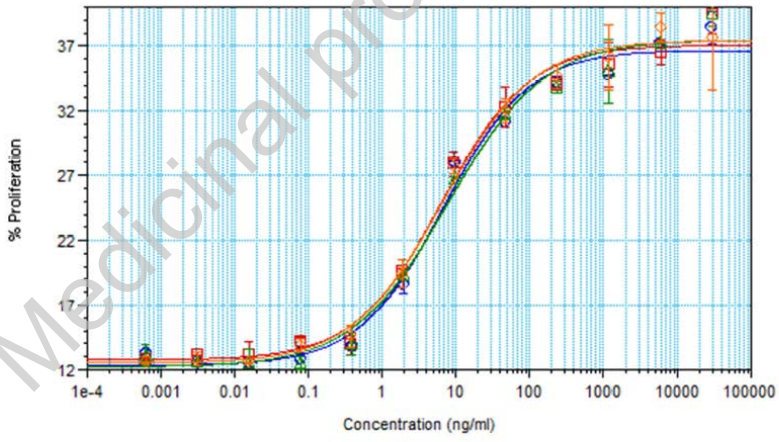


Mitogenic Potential of MK-1293 and Lantus: Run 1. Values are presented as mean of triplicates ± standard error of the mean. CPM = counts per minute.

Data from Study PD007 (EU-Lantus)

The mitogenic potential of MK-1293 and **EU-Lantus** was assessed in a 5-ethynyl-2'-deoxyuridine (EdU) uptake assay in Saos-2/B10 cells.

The mean relative potency values of MK-1293 for induction of mitogenesis ranged from 86% to 116%. The mean relative potency values of Lantus for induction of mitogenesis ranged from 87% to 114%. The 95% CI for MK-1293 were within those for Lantus. The results of a representative run are presented in the figure below. The similarity between MK-1293 and EU-Lantus in respect to mitogenicity could be clearly shown. Mitogenicity is an off-target effect of insulin so that it is not fully within the scope of biosimilarity. Nevertheless, the findings shown above further confirm similarity between MK-1293 and EU-Lantus.



Induction of Mitogenesis by MK-1293 and Lantus: Dose-response. Curves are from a representative run

In vivo studies

In-vivo studies are usually not required for a biosimilar insulin application. Nevertheless, the Applicant has studied in vivo PD in two animal models of diabetes, rats treated with streptozotocin (STZ, Study PD002) and dogs treated with somatostatin (Study PD003).

STZ rats

Study PD002

Effects of MK-1293 and **US-Lantus** on levels of blood glucose were assessed in the streptozotocin-induced rat model of human type I diabetes mellitus. Plasma levels of glucose and insulin glargine were determined at different time points up to 24 hours after the (single) injection of MK-1293 or Lantus.

Levels of blood glucose following administration of MK-1293, Lantus, or vehicle are presented in the figure below. The AUC_{0-24h} values for glucose and the glucose AUC_{0-24h} ratios for MK-1293 to Lantus ranged from 0.85 to 0.97. The figure shows a good comparability of MK-1293 and Lantus at the mid and high dose level. At the lowest dose (1 U/kg) the glucose-lowering effect of MK-1293 was stronger than that of Lantus for unknown reasons.

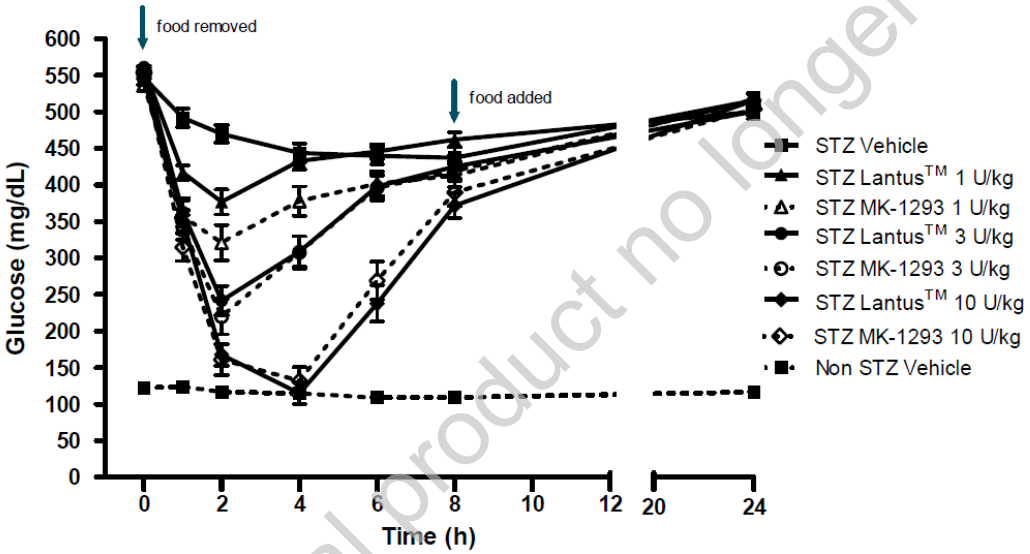


Figure 1 Levels of Glucose in Blood Following Administration of MK-1293, Lantus, or Vehicle. The data presented are pooled from 4 studies. Values are presented as mean ± standard error of the mean. Non-STZ Vehicle = animals administered formulation buffer for MK-1293 and Lantus and formulation buffer for STZ; STZ = streptozotocin; STZ Lantus = animals administered Lantus and STZ; STZ MK-1293 = animals administered MK-1293 and STZ; STZ Vehicle = animals administered STZ and formulation buffer for MK-1293 and Lantus.

This study also included a comparison of PK data. Levels of MK-1293 and Lantus over time were generally similar for the doses tested (1, 2 and 10 U/kg). The AUC_{0-6h} ratios of MK-1293 to Lantus ranged from 0.94 to 1.07.

Somatostatin-treated dogs

Study PD003

Effects of MK-1293 or **US-Lantus** on levels of glucose in plasma were assessed in the somatostatin-induced dog model of human type I diabetes mellitus. Somatostatin inhibits secretion of insulin, which results in

hyperglycaemia in the absence of exogenous insulin. Two cohorts of animals were tested, each cohort consisting of 4 to 6 dogs per treatment group (MK-1293 and three batches of US-Lantus).

The glucose AUC_{0-24h} ratios for MK-1293 to Lantus ranged from 1.00 to 1.08 for animals in Cohort 1 and from 0.72 to 0.82 in Cohort 2. In Cohort 2, a higher dose of MK-1293 (0.33 instead of 0.3 U/kg) was administered by error. This can explain these lower glucose AUCs observed with MK-1293 as compared to Lantus.

Plasma levels of insulin glargine over time after administration of MK-1293 or Lantus were also determined. In Cohort 2 MK-1293 was dosed higher than Lantus by error. Accordingly, higher plasma concentrations of MK-1293 than of Lantus were observed. Also in Cohort 1, with correct dosing, MK-1293 reached slightly higher plasma levels than all batches of Lantus tested. The reason is unclear but this is no concern since in-vivo studies are not regarded suitable for demonstrating biosimilarity.

2.3.2. Pharmacokinetics

PK studies in animals are usually not required for a biosimilar application. PK data were also obtained within the frame of the in-vivo PD studies (see above) and the toxicology studies (see below). In the two dedicated PK studies, the focus was on the metabolites of insulin glargine, i.e. glargine molecules lacking 1 to 3 amino acids at the C-terminus of the B-chain.

Study PK001, "Pharmacokinetic Studies of MK-1293 in Rats and Dogs"

MK-1293 was compared with **US-Lantus** in pharmacokinetics in Sprague Dawley rats and pharmacokinetics and injection site disposition kinetics in Beagle dogs.

MK-1293 was cleared from the systemic circulation with a short apparent terminal t½ of 1.1 hr. The systemic exposure (AUC), maximal drug concentration (C_{max}), and time of maximum drug concentration (T_{max}) of MK-1293 are comparable to those of Lantus, indicating a similar extent of SC absorption in this species.

SC deposition and pharmacokinetics of a radiolabeled ([^{125}I]-MK-1293) were evaluated in Beagle dogs and compared to that of [^{125}I]-Lantus and [^{125}I]-Humulin R (regular insulin). Following SC administration in dogs at 0.3 U/kg, [^{125}I]-MK-1293 (as measured by acid precipitable radioactivity) cleared from the systemic circulation with an apparent terminal t½ of 41.5 hr. The terminal t½, systemic exposure (AUC), and maximal drug concentration (C_{max}) of MK-1293 are comparable to that of [^{125}I]-Lantus. As anticipated, [^{125}I]-Humulin R (regular insulin) cleared much faster with a terminal t½ of 16.1 hr. The time for 50% of the radioactivity to leave the injection site (T50%) was 6.3, 6.1, and 1.2 hr for [^{125}I]-MK-1293, [^{125}I]-Lantus, and [^{125}I]-Humulin R, respectively, consistent with SC drug deposition and extended-release for MK-1293 and Lantus. These data support the delayed absorption and a longer duration of action characteristics for MK-1293 relative to Humulin R, and comparable to that of Lantus.

Study PK002, "Metabolism Studies of MK-1293"

This study contains three parts. First, in-vivo metabolism of MK-1293 vs. **US-Lantus** in rats, second, in-vitro metabolism of these test products in blood plasma of different species (rat, dog, human) and, third, stability of MK-1293 and Lantus in rat, dog and human plasma. Two primary active metabolites (M1 and M2) and a minor active metabolite (M) were reported for Lantus in humans both at the injection site and in circulating plasma. These metabolites are derived from the sequential loss of the engineered arginines and the threonine residue from the C-terminus of the B-chain to result in loss of 1 (Arg), 2 (Arg-Arg), and 3 (Arg-Arg-Thr) amino acids, generating metabolites M, M1, and M2, respectively.

Following subcutaneous administration of MK-1293 or US-sourced Lantus at 10 U/kg to rats, M1 was identified as the major circulating metabolite from both parent compounds. The plasma levels of M1 derived from MK-1293 were comparable to that from US-sourced Lantus at each sampling time point and similar levels of the parent compounds were also detected between MK-1293 and US-sourced Lantus dosed groups, suggesting that MK-1293 and US-sourced Lantus underwent similar disposition and metabolism in rats.

An in vitro metabolism experiment was conducted to compare the metabolite formation after spiking MK-1293 (Lot #NB196-124) or US-sourced Lantus (Lot #40C245) into fresh rat, dog, and human plasma. As shown in Figure 2, a primary metabolite (M1) and two minor metabolites (M and M2) were found in the rat plasma, whereas only M1 and M were detected in the plasma of dog and humans. The levels of the metabolites identified were comparable between MK-1293 and US-sourced Lantus spiked samples, suggesting similar in vitro metabolism of both compounds across species.

MK-1293 (non-GMP Lot #NB196-164) or US-sourced Lantus™ (Lot #40C245) were spiked into fresh rat, dog, and human plasma at a lower concentration relative to the in vitro metabolism studies, and parent compounds were measured with LCMS. MK-1293 parent stability was similar to that of US-sourced Lantus across rat, dog, and human plasma with ~75% of parent remaining after 1 hour at 37°C.

2.3.3. Toxicology

Toxicology studies are not required for a biosimilar application unless there is cause for concern. Despite this, two repeated-dose studies of 1 month duration and a 7-day pilot study were performed. Single dose toxicity studies were not performed. Notably, repeated-dose toxicity studies were not conducted in direct comparison of MK-1293 to comparator Lantus. Instead, MK-1293 and EU-approved Lantus were tested in two different studies, albeit with identical design. The following table provides an overview of the studies performed.

Table 5: Toxicology Programme

Study Type/Duration	Route	Species	Dose Levels (mg/kg/day)	NOAEL (mg/kg)	Study No. (GLP Status)
Repeat-dose toxicity					
Toxicity/7-day	SC	Rat	0.15, 0.5 or 1.5 (MK-1293 or EU-approved Lantus)	0.5 (both MK-1293 and EU-approved Lantus)	TT #10-1024 (Non-GLP)
Toxicity/ 1 month with a Four-week Treatment Free Period	SC	Rat	0.15, 0.5 or 1.5 MK-1293	0.5	TT #10-1088 (GLP)
Toxicity/ 1 month with a Four-week Treatment Free Period	SC	Rat	0.15, 0.5 or 1.5 EU-approved Lantus	0.5	TT #10-1089 (GLP)
NOAEL = No observed adverse effect level; GLP = Good Laboratory Practices; SC = Subcutaneous					

Exploratory 7-Day Subcutaneous Tolerability Study in Female Rats (TT #10-1024)

Thirty-Eight Crl:WI(HAN) female rats were assigned to 3 dose groups given MK-1293 or Lantus in doses of 0.15, 0.5 or 1.5 mg/kg/day or 1 control group. Assessment of toxicity was based on mortality, clinical observations, body weights, and clinical and anatomic pathology evaluations. Plasma MK-1293 and Lantus drug concentrations in treated and control samples were determined using a radioimmunoassay.

The findings were in line with the observations made in the 1-month studies (see below).

1-month studies TT #10-1088 and TT #10-1089

MK-1293 and Lantus were not compared head-to-head in one study; instead, MK-1293 was tested in ascending doses in study TT #10-1088 whereas Lantus was tested (at the same doses) in study TT #10-1089

MK-1293 (Study TT #1088) or **Lantus** (Study TT #1089) were administered subcutaneously to rats daily at doses of 0.15, 0.5 or 1.5 mg/kg/day for approximately 4 weeks followed by an approximate 4-week treatment-free period. The original study design included 10 rats/sex/group designated for interim necropsy (following 4 weeks of dosing) along with 5 rats/sex/group designated for final necropsy (following a 4-week treatment-free period). An additional 12 rats/sex/group (24 rats total) were designated for toxicokinetic evaluation only.

MK-1293: Test article-related deaths occurred only at 1.5 mg/kg/day. At this dose, **6 animals**, three females and 3 males, were found dead (prior to dosing) on Study Day 4. Due to this high mortality at 1.5 mg/kg/day, all remaining high-dose animals were terminated early or placed on recovery. Twelve animals, originally designated for toxicokinetic evaluation, were subsequently re-designated for the main toxicity arm (1.5 mg/kg/day group). After re-designating these animals, a total of **5 of these additional animals**, 2 females and 3 males, were found dead prior to, or on the morning of interim necropsy (Study Days 18, 24, 28, and 31). In general, test article-related physical signs were not observed prior to death, and acute hypoglycaemia, an expected exaggerated pharmacodynamic effect, was considered a likely cause of death.

Lantus: There were **11 cases** of test article-related unscheduled deaths at 1.5 mg/kg/day only. In general, these rats did not show test article-related physical signs prior to their deaths. The possible cause of death of these animals was expected exaggerated pharmacodynamic effect (hypoglycaemia).

All other findings were in line with known actions of insulin and revealed no relevant differences between MK-1293 and Lantus as far as conclusions are possible across two different studies. There were no unexpected findings with MK-1293 which could give a cause for concern.

Immunogenicity

In the MK-1293 study a rather high percentage of animals (12.5%) were antibody-positive already at Day 0 for unknown reasons. Thereafter, the percentage of antibody-positive animals increased up to 38.8%. In the Lantus study, the increase was stronger, up to 59.7%. In the MK-1293 study, antibody formation was clearly dose-dependent whereas in the Lantus study the low- and high-dose group developed antibodies in equal percentage. Thus, there were some differences in antibody induction by MK-1293 and Lantus, respectively. However, this is not considered relevant because, first, cross-study comparison is difficult and, second, immunogenicity in animals is usually not predictive of the response in humans.

Toxicokinetics

Insulin glargine concentration was determined by a RIA which employs radiolabelled human insulin as a tracer and guinea pig anti-human insulin antibodies. The assay was validated with respect to accuracy and precision, dilutional linearity and specificity (matrix effect). The pre-defined acceptance criteria were met. Comparable reactivity of MK-1293 and Lantus could be demonstrated. Sample stability for 24 h at 2-8 °C and freeze and thaw-stability over 5 cycles could be shown as well as long-term stability of the reference standard.

There were numerical differences in the TK parameters of MK-1293 and Lantus, respectively. The reason is unclear, but considering that MK-1293 and Lantus were tested in different studies this is not regarded as a concern. Comparability across studies is always difficult. Although for demonstrating biosimilarity head-to head comparison of biosimilar and reference product is strongly encouraged, for this reason it has to be considered

that toxicity studies are usually not necessary for showing biosimilarity. There are no concerns in the case of MK-1293 which would require a toxicology study. Therefore, the presented toxicology programme is considered supportive and did not yield unexpected findings.

2.3.4. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified as follows: Insulin glargine is a recombinant human basal insulin analog produced in *Escherichia coli*. According to the EMEA/CHMP/SWP/4447/00 guideline 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 non-clinical comparability exercise was done in first experiments with Lantus sourced from USA and, in consecutive studies, with Lantus sourced from EU. Analytical data show that US-Lantus is representative for EU-Lantus and that the MK-1293 material used in earlier studies is considered comparable to the final material. Hence, results from the earlier studies using US-Lantus are relevant for the biosimilarity exercise.

The Applicant tested biosimilarity of MK-1293 and the comparator EU-Lantus at all required levels, i.e. receptor binding, receptor activation (i.e. receptor autophosphorylation) and metabolic function (glucose uptake, inhibition of glucose production and inhibition of lipolysis). Furthermore, binding to the IGF-1 receptor and mitogenicity in cultured tumour cells were studied. In general, corresponding data points from MK-1293 and Lantus were close together and could be fitted well to a sigmoid concentration-response curve. This demonstrates good quality of the results and high similarity of MK-1293 and Lantus. For receptor binding studies of MK-1293 in comparison to US-Lantus, a classical cell-based assay (CHO cells expressing recombinant human IR, either isoform IR-A or isoform IR-B) was used. In contrast, for binding studies with EU-Lantus, a Biacore-based assay was employed which requires the use of a soluble IR fragment instead of the native receptor protein. This assay also allowed discrimination between IR-A and IR-B. For investigating IR autophosphorylation, native HepG2 human liver carcinoma cells were used for comparison of MK-1293 with US-Lantus whereas CHO cells overexpressing human IR-A or IR-B were used for EU-Lantus. The different methodical approaches used for US- and EU-Lantus are complementary and have all specific advantages and disadvantages. There is no clear preference so that all methods used are acceptable.

According to current understanding, the IR-B isoform is mainly responsible for mediating the metabolic actions of insulin whereas IR-A appears to be more involved in mediating proliferative actions of insulin. Hence, in respect to the therapeutic use of insulin, measuring binding to and activation of IR-B selectively seems to be more important. On the other hand, it is not known whether the experimental approaches needed for targeting IR-A and IR-B separately are indeed more sensitive and more predictive for the situation in patients than using cells spontaneously expressing insulin receptors in the native cellular environment, e.g. HepG2 cells as described above. However, this is no concern since the Applicant has followed both approaches, and both confirmed similarity between MK-1293 and Lantus.

The Applicant performed three different functional assays of IR activation, glucose uptake, inhibition of glucose production and inhibition of lipolysis, in permanently cultured cells. With each assay plausible concentration-response relationships were obtained. In all cases MK-1293 behaved similar to Lantus.

Some animal PK data were provided although not required for a biosimilar application. The data do not raise any concerns. MK-123 and Lantus behaved generally similar in respect to the parameters measured.

The Applicant investigated repeated-dose toxicity of MK-1293 and Lantus in two separate 1-month-studies, one for MK-1293 and one for Lantus. This is unusual since head-to head comparison in one study is desirable and comparison across studies is less reliable. However, toxicity studies are not required for biosimilar products unless there is cause for concern, e.g. findings in the pharmaceutical part or a new production process; which is not the case here. The toxicology results met the expectations with unscheduled deaths in the high dose groups, obviously due to hypoglycaemia.

2.3.6. Conclusion on non-clinical aspects

The Applicant has provided an extensive comparability exercise at the non-clinical level, showing good comparability of MK-1293 and Lantus.

2.4. Clinical aspects

2.4.1. Introduction

- Tabular overview of clinical studies

Protocol Number	Objectives	Design	Population/ Enrolled (completed[1])	Study Drugs (dosing device)
Phase I[2]				
001	Pilot PD and PK comparison between MK-1293 and EU-approved Lantus	Single dose, double-blind, randomized, 2-period, complete crossover euglycemic clamp	Healthy males; 18 to 45 years N: 24 (23)	MK-1293 Cartridge formulation[3] (insulin syringe) EU-approved Lantus Cartridge formulation (insulin syringe)
002	1) PD and PK similarity demonstration between MK-1293 and EU-approved Lantus 2) PD and PK similarity demonstration between MK- 1293 and US-approved Lantus 3) PD and PK comparability demonstration between EU- and US-approved Lantus	Single dose, double-blind, randomized, 3-period crossover euglycemic clamp	Healthy males; 18 to 45 years N: 109 (96)	MK-1293 Cartridge formulation[4] (insulin syringe) EU-approved Lantus Cartridge formulation (insulin syringe) US-approved Lantus Cartridge formulation (insulin syringe)
005	PD and PK similarity demonstration between MK-1293 and EU-approved Lantus in T1DM subjects	Single dose, double-blind, randomized, 2-treatment, 4-period replicate crossover euglycemic clamp study	Males and females with T1DM; 18 to 65 years N: 76 (70)	MK-1293 Cartridge formulation[4] (insulin syringe) EU-approved Lantus Cartridge formulation (insulin syringe)
008	Formulation bridging PK comparison between the vial and cartridge formulations of MK-1293	Single dose, double-blind, randomized, 2-period, complete crossover euglycemic clamp	Healthy males; 18 to 45 years N: 46 (42)	MK-1293 Cartridge formulation[4] (insulin syringe) MK-1293 Vial formulation[4] (insulin syringe)
Phase III[5]				
003	52-Week (Phase A is 24 weeks and Phase B is 28 weeks) Efficacy and Safety comparing MK-1293 and EU-approved Lantus in T1DM subjects	multinational, randomized, open-label, parallel group safety and efficacy comparison	Males and females with T1DM; >18 years N: 502 (495)	MK-1293 Cartridge formulation[4] (clinical reusable pen) EU-approved Lantus Cartridge formulation (TactiPen™)
006	24-Week Efficacy and Safety comparing MK-1293 and EU-approved Lantus in T2DM subjects	multinational, randomized, open-label, parallel group safety and efficacy comparison	Males and females with T2DM; >18 years N: 528 (485)	MK-1293 Cartridge formulation[4] (clinical reusable pen) EU-approved Lantus Cartridge formulation (TactiPen™)

[1] Number of subjects completing all treatment periods
[2] The dose of all study drugs in all Phase I studies was 0.4 units/kg, administered by single SC injection in the abdomen
[3] Early stage (pre-commercial) drug product
[4] Late stage (representative commercial) drug product
[5] MK-1293 dosing in both Phase III studies was conducted with a clinical reusable pen device, not the commercial combination product.

GCP

The Clinical 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.

2.4.2. Pharmacokinetics

Insulin glargine is a recombinant human basal insulin analogue produced in Escherichia coli (E. coli) and marketed worldwide by Sanofi under the trade name Lantus. MK-1293 is an insulin glargine being developed by the Applicant as a biosimilar, with Lantus as the chosen reference medicinal product. MK-1293 has the same amino acid sequence as Lantus and, like Lantus; MK-1293 is produced in E. coli.

The MK-1293 clinical pharmacology programme consisted of four studies, all of which were single dose crossover euglycaemic clamp studies. These included two studies conducted to demonstrate definitive PD and PK similarity between representative commercial MK-1293 cartridge formulation DP and Lantus, P002 in healthy subjects and P005 in T1DM subjects.

For quantitate determination of glargine, and its active metabolites (M1 and M2) an LC-MS/MS assay was developed. The assay was validated over the concentration range of 100-10,000 picograms (pg)/mL in human plasma. PK parameter values were calculated only for active metabolite M1 (the primary circulating glargine species).

P002 was a single dose, double-blind, three-period three-treatment, balanced crossover euglycaemic clamp study in healthy subjects (total enrolment was 109 subjects). In each treatment period, subjects received 1 of 3 single-dose treatments (MK-1293, US-Approved Lantus or EU-Approved Lantus) in a randomized order. The Trial centre was the Profil Institute for Clinical Research, Chula Vista, CA, USA.

PK objectives

Primary: M1 glargine metabolite profiles of MK-1293, US-Approved Lantus and EU-Approved Lantus after single 0.4 units/kg SC doses with regards to the area under the curve over the first 24 hours after dosing (AUC_{0-24}) and maximal concentration (C_{max}).

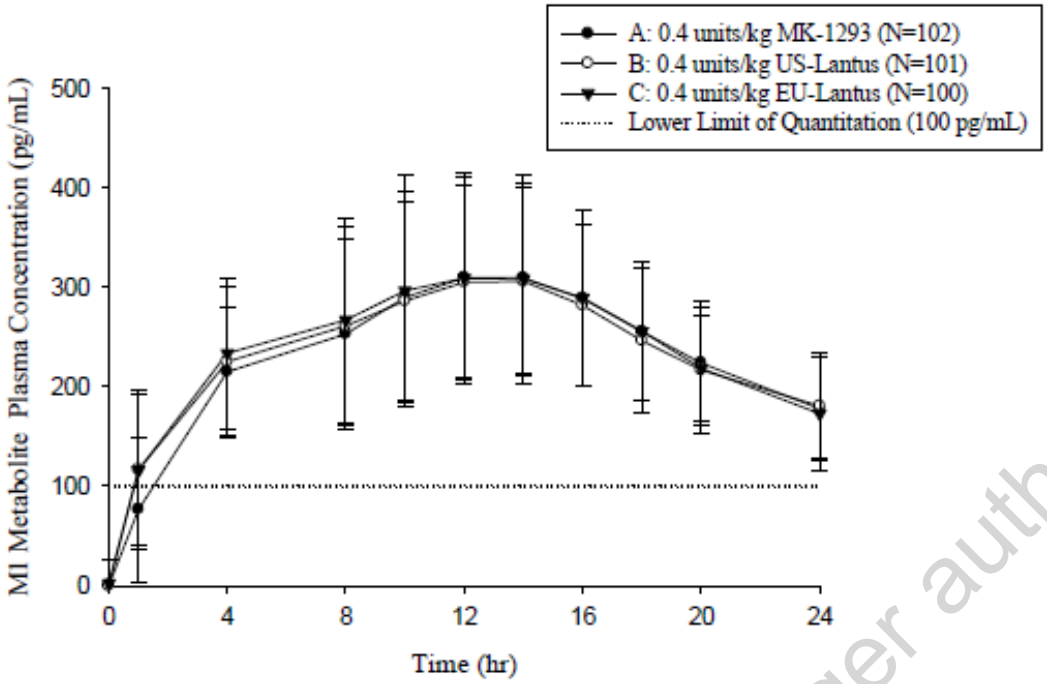
Secondary: M1 glargine metabolite profiles of MK-1293, US-Approved Lantus and EU-Approved Lantus after single 0.4 units/kg SC doses with regards to subfractions of the 24 hours after dosing (AUC_{0-12}, and AUC_{12-24}).

Statistical analysis of PK data

Individual glargine (M1 metabolite) AUC_{0-24} and C_{max} values were natural log-transformed and analysed separately with a linear mixed effects model with fixed effects terms for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same subject. A 90% confidence interval for the difference in treatment means for all pairwise treatment comparisons on the log scale was calculated using the mean square error from the model and referencing a t-distribution for each endpoint. These confidence limits were exponentiated to obtain the 90% confidence interval for the geometric mean ratio for each of the three treatment comparisons for AUC_{0-24} and C_{max}.

The 90% confidence intervals for both AUC_{0-24} and C_{max} for a given treatment comparison need to lie within (0.80, 1.25) to conclude equivalence.

Results:



PK Endpoint	MK-1293 N†	MK-1293 GM (95% CI)	US Lantus N‡	US Lantus GM (95% CI)	EU Lantus N	EU Lantus GM (95% CI)	Geometric Mean Ratio (90% CI) (MK-1293/ US Lantus)	(MK-1293/ EU Lantus)	(EU/ US Lantus)
AUC0-24hr § (pg·hr/mL)	102	5335 (4994, 5699)	100	5455 (5169, 5757)	100	5526 (5219, 5850)	0.98 (0.93, 1.03)	0.97 (0.92, 1.02)	1.01 (0.97, 1.05)
Cmax § (pg/mL)	102	323 (305, 343)	100	319 (301, 339)	100	323 (303, 344)	1.01 (0.96, 1.07)	1.00 (0.95, 1.05)	1.01 (0.96, 1.06)
AUC0-12hr § (pg·hr/mL)	102	2415 (2256, 2584)	101	2539 (2380, 2709)	100	2583 (2412, 2765)	0.95 (0.90, 1.01)	0.93 (0.89, 0.98)	1.02 (0.97, 1.07)
AUC12-24hr § (pg·hr/mL)	102	2927 (2765, 3100)	100	2880 (2739, 3028)	100	2909 (2760, 3065)	1.02 (0.97, 1.07)	1.01 (0.96, 1.05)	1.01 (0.97, 1.05)

† One subject with all values BLQ through first 12 hours, 1/2 LOQ imputed for timepoints needed to calculate AUC_{0-12hr} (See Section 10.4)
‡ One subject discontinued ~16 hours after dosing; only AUC_{0-12hr} was calculated for this subject (See Section 10.4)
§ Analysis performed on log scale, results back transformed to original scale
GM=Geometric Mean

Since 90% confidence intervals for the geometric mean ratios for both primary PK endpoints (M1 glargine metabolite AUC_{0-24hr} and C_{max}) for all three treatment comparisons lie within (0.80, 1.25), the primary PK hypotheses are supported. For the secondary PK endpoints (M1 glargine metabolite AUC_{0-12hr} and $AUC_{12-24hr}$), the 90% confidence intervals for the geometric mean ratios lie as well within (0.80, 1.25).

P005 was a single dose, double-blind, 2-treatment, 4-period replicate crossover trial isoglycaemic clamp study in subjects with type I diabetes mellitus (T1DM; total enrolment was 76 subjects). In each period, subjects received 1 of 2 subcutaneous (SC) single-dose treatments (MK-1293 or EU-Approved Lantus) in a randomized order.

PK objectives

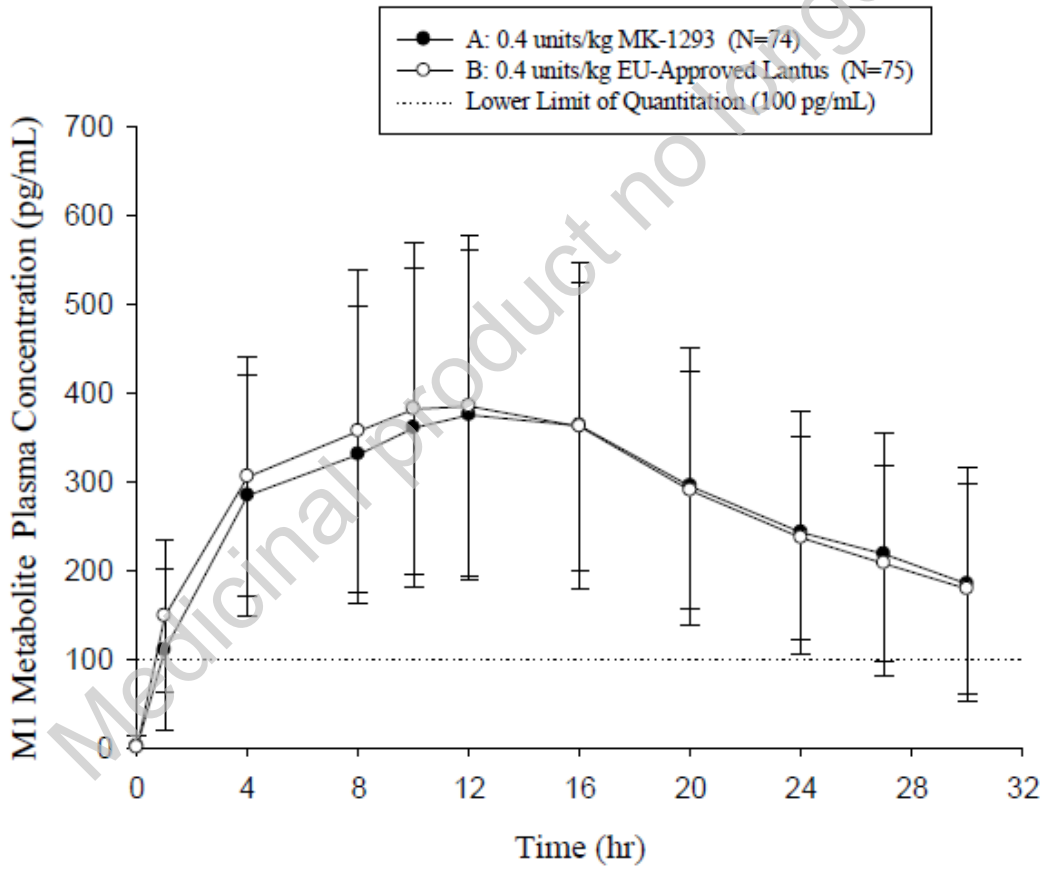
Primary: M1 glargine metabolite profiles of MK-1293 and EU-Approved Lantus after single 0.4 units/kg SC doses to subjects with T1DM with regards to the area under the curve over hours 24 hours after dosing ($AUC_{0-24hrs}$) and maximal concentration (C_{max}).

Secondary: M1 glargine metabolite profiles of MK-1293 and EU-Approved Lantus after single 0.4 units/kg SC doses to subjects with T1DM with regards to sub-fractions of the 24 hours after dosing (AUC_{0-12} and AUC_{12-24}).

Statistical analysis of PK data

Individual glargine (M1 metabolite) AUC_{0-24} and C_{max} values (and partial AUC values) were natural log-transformed and analysed separately with a linear mixed effects model with fixed effects terms for treatment, period and sequence. An unstructured covariance matrix was used to allow for unequal between subject variances for both treatments and to model the correlation between different treatments within the same subject. Moreover, separate within subject variances for each treatment were modelled. 90% confidence intervals were constructed as for study P002 and need to lie within (0.80, 1.25) to conclude equivalence.

Results:



PK Endpoint	MK-1293		EU-Lantus		Geometric Mean Ratio (90% CI) (MK-1293 / EU-Lantus)	Within Subject % CV ‡	
	N †	GM (95% CI)	N †	GM (95% CI)		MK-1293	EU-Lantus
AUC0-24§ (pg·hr/mL)	74	6530 (5967, 7145)	75	6763 (6162, 7423)	0.97 (0.91, 1.02)	23.6	31.6
Cmax§ (pg/mL)	74	372 (339, 408)	75	382 (350, 416)	0.97 (0.93, 1.03)	26.4	27.8
AUC0-12§ (pg·hr/mL)	74	2981 (2714, 3274)	75	3251 (2968, 3562)	0.92 (0.86, 0.97)	28.4	32.7
AUC12-24§ (pg·hr/mL)	74	3510 (3205, 3845)	75	3522 (3228, 3844)	1.00 (0.95, 1.04)	21.7	24.5
Tmax‖ (hr)	74	12.5 (4.0, 21.5)	75	12.0 (4.0, 23.0)	.	.	.

† Number of subjects with at least one administration of the particular treatment
‡ Within-Subject Percent CV calculated as square root of the residual error for each treatment from mixed effects model appropriate for replicate crossover design
§ Analysis performed on log scale, results back transformed to original scale
‖ Median (Min, Max) (Calculated after taking the median of Tmax values across the replicates for given subject and treatment)
GM=Geometric Mean

Since the 90% confidence intervals for the geometric mean ratios for both primary PK endpoints (M1 glargine metabolite AUC_{0-24} and C_{max}) lie within (0.80, 1.25), the primary hypothesis that the PK profiles of MK-1293 and EU-Approved Lantus are similar following single 0.4 units/kg SC doses to subjects with T1DM is supported. For the secondary PK endpoints (M1 glargine metabolite AUC_{0-12hr} and $AUC_{12-24hr}$), the 90% confidence intervals for the geometric mean ratios lie as well within (0.80, 1.25).

2.4.3. Pharmacodynamics

In clinical studies, intravenous administration of equimolar amounts of insulin glargine and human insulin produced pharmacodynamic profiles that were approximately the same, indicating similar PD properties once in systemic circulation. After subcutaneous (SC) administration, the insulin glargine time x action profile correlates closely with the protracted PK profile described above, resulting in a relatively flat PD profile with effects typically lasting ≥ 24 hours.

As with all insulins, insulin glargine exerts its pharmacodynamic effects through binding to the insulin receptor at target tissues including liver, skeletal muscle, and adipose. The glucose-lowering effects of pharmacologic insulins are achieved through inhibiting hepatic glucose production and promoting glucose uptake in peripheral tissues, primarily skeletal muscle and adipose.

The time-action profiles of MK-1293 and the reference product Lantus were compared in the two clamp studies P002 and P005. Bedside glucose measurement was performed with a GlucoScout and a YSI 2300 STAT Plus was used to confirm the accuracy of the GlucoScout real time blood glucose monitor at hourly intervals.

P002 (healthy subjects):

Fasting (overnight for ~10 hours) subjects were connected to the automatic blood glucose analyser for at least 1 hour prior to time 0 of the clamp procedure. The FPG must be > 70 mg/dL and < 100 mg/dL at -3 minute timepoint prior to dosing.

Onset of insulin action was identified by a sustained ~ 5% decline of glucose concentration from the fasting level. After the onset of insulin action had been identified, glucose infusion was then utilized as needed to maintain glucose concentration at ~ 80 mg/dl.

Primary objective was to compare the PD profiles of MK-1293, US-Approved Lantus and EU-Approved Lantus after single 0.4 units/kg SC doses with regards to the area under the glucose infusion rate (GIR) versus time curve (GIR-AUC_{0-24}, GIR-AUC_{0-12}, and GIR-AUC_{12-24}) and the maximal glucose infusion rate (GIR_{max}).

Individual GIR-AUC_{0-24}, GIR-AUC_{0-12}, GIR-AUC_{12-24} and GIR_{max} (where GIR_{max} was based on LOESS smoothed data) were analysed with the linear mixed model described for PK data (study P002). Fieller's Theorem was used to calculate 90% confidence intervals for the ratio of arithmetic means for each endpoint and treatment comparison using results from the linear mixed effects model and referencing a t-distribution.

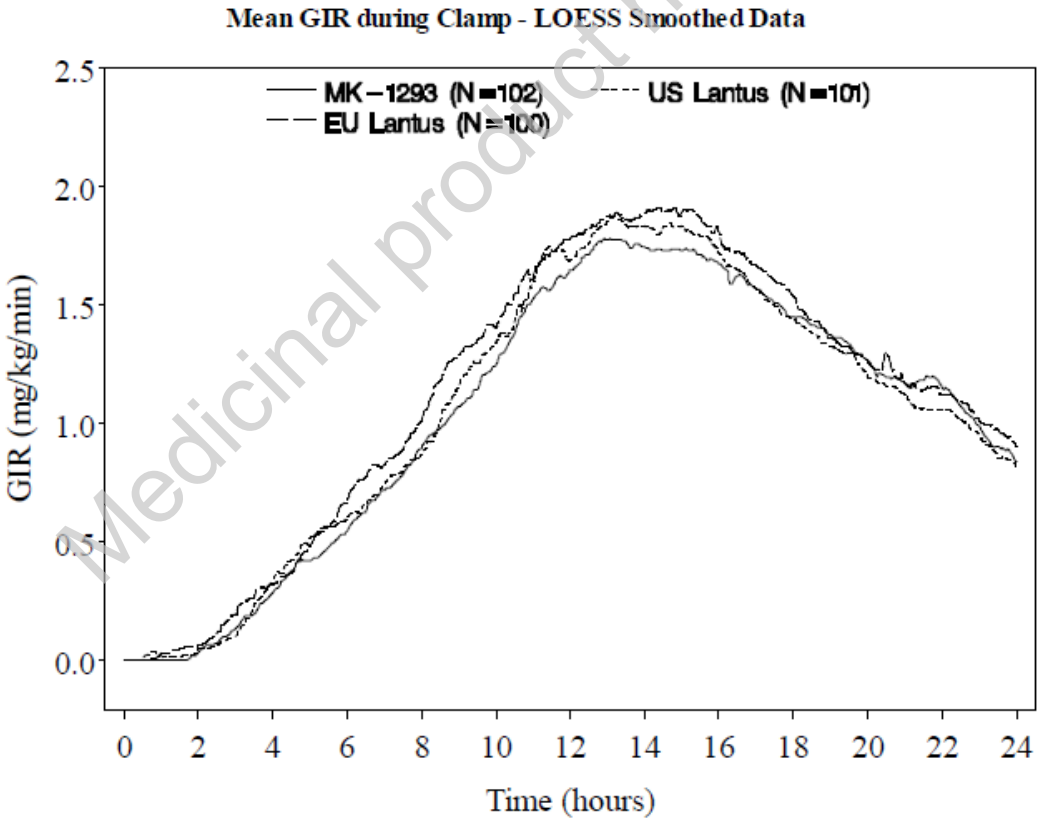
If the 90% confidence intervals for all four defined endpoints for a given treatment comparison lie within (0.80, 1.25), then the primary PD hypothesis corresponding to that particular treatment comparison would be supported.

Additionally, 95% confidence intervals are provided.

It should be noted that within the pharmacodynamics hypothesis and within the pharmacokinetic hypothesis no multiplicity adjustment is applied, since the mean treatment ratio for each endpoint needs to lie within (0.8, 1.25) to support the particular primary hypothesis.

Moreover, no multiplicity adjustment is being applied across primary hypotheses as each need to be met in order to claim similarity/comparability among study drugs.

Results



PD Endpoint	MK-1293		US Lantus		EU Lantus		Ratio of Arithmetic Means (95% CI) ‡		
	N	Mean (95% CI)	N †	Mean (95% CI)	N	Mean (95% CI)	(MK-1293/ US Lantus)	(MK-1293/ EU Lantus)	(EU Lantus / US Lantus)
GIR AUC0-24hr (mg/kg)	102	1533.12 (1296.33, 1769.92)	100	1517.27 (1299.26, 1735.29)	100	1598.09 (1355.67, 1840.50)	1.01 (0.91, 1.12)	0.96 (0.87, 1.05)	1.05 (0.95, 1.16)
GIR AUC0-12hr (mg/kg)	102	475.87 (376.56, 575.18)	101	495.87 (400.16, 591.58)	100	522.58 (413.35, 631.82)	0.96 (0.82, 1.11)	0.91 (0.798, 1.04)	1.05 (0.91, 1.22)
GIR AUC12-24hr (mg/kg)	102	1055.07 (912.03, 1198.11)	100	1023.57 (891.55, 1155.59)	100	1075.60 (931.28, 1219.92)	1.03 (0.93, 1.14)	0.98 (0.90, 1.07)	1.05 (0.96, 1.15)
GIRmax § (mg/kg/min)	102	2.26 (1.94, 2.59)	100	2.36 (1.99, 2.73)	100	2.48 (2.10, 2.87)	0.96 (0.86, 1.08)	0.91 (0.83, 1.01)	1.05 (0.93, 1.20)

† One subject discontinued ~15 hours after dosing, only GIR AUC0-12 and Onset of Action were calculated for this subject (See Section 10.4)
‡ 95% confidence interval for ratio of arithmetic means calculated via Fiellers Theorem
§ Determined from smoothed data

P005 (subjects with T1DM):

An overnight IV insulin infusion (insulin aspart) was initiated approximately 10 hours prior to trial drug administration (after evening snack). The aspart infusion was titrated to target a stable glucose concentration of ~130 mg/dL without administration of exogenous glucose for as long as possible prior to dosing.

After dosing, the insulin infusion was weaned as appropriate to maintain glucose concentrations at ~ 130 mg/dL. Once the insulin infusion had been weaned off, onset of insulin action was identified by a sustained ~ 5% decline of glucose concentration from the target of ~ 130 mg/dL. After the onset of insulin action had been identified, glucose infusion was then utilized as needed to maintain glucose concentration at ~ 130 mg/dL.

The primary objectives were the same as in P002 but with an additional comparison of the duration of action (DOA) of Lantus and MK-1293.

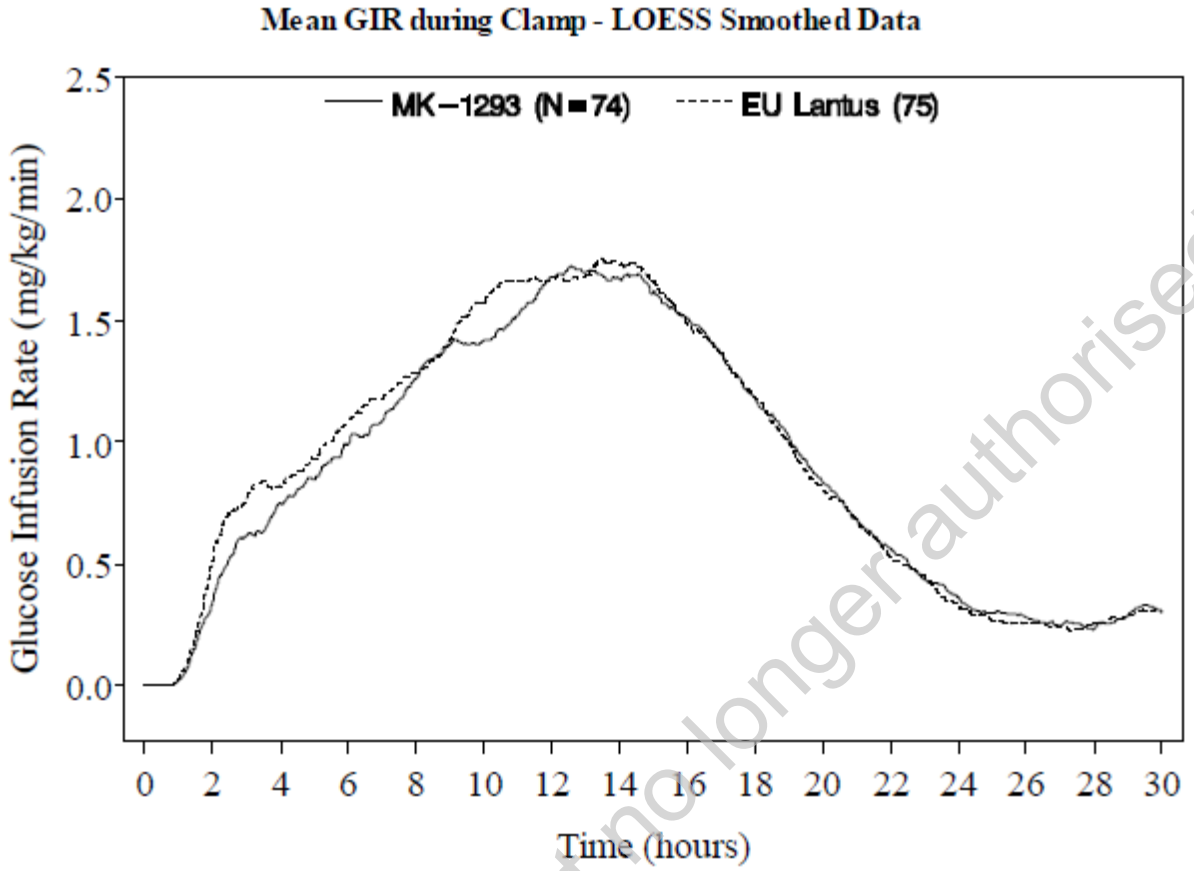
Individual GIR-AUC_{0-24}, GIR-AUC_{0-12}, GIR-AUC_{12-24} and GIR_{max} (where GIR_{max} was based on LOESS smoothed data) were analysed with the linear mixed model described for PK data (study P005). Fieller's Theorem was used to calculate 95% confidence intervals for the ratio of arithmetic means for each parameter and treatment comparison using results from the linear mixed effects model and referencing a t-distribution.

Duration of Action (DOA) was planned to be analysed in a similar fashion as the other pharmacodynamics parameters. However, the Duration of Action (DOA) comparison could not be conducted as specified due to the high proportion of individuals not achieving end of PD action during the 30 hour clamp timeframe. In order to take into account the right censored data for DOA (i.e., those who did not achieve end of action in the timeframe studied), a survival analysis approach was defined post hoc. A frailty model was used with effects for treatment, period and sequence and a random effect for subject. From this model, the hazard ratio and Wald 95% confidence intervals for treatment were obtained. A value of 1.00 for the hazard ratio corresponds to no difference between treatments.

The 95% confidence intervals for all PD endpoints for a given treatment comparison need to lie within (0.80, 1.25) to conclude equivalence.

As for study P002, no multiplicity adjustment is applied within pharmacodynamics/pharmacokinetics hypotheses as well as across primary hypotheses.

Results



PD Endpoint	MK-1293		EU-Lantus		Ratio of Arithmetic Means (95% CI) ‡	Within Subject % CV	
	N †	Mean (95% CI)	N †	Mean (95% CI)	(MK-1293 / EU-Lantus)	MK-1293	EU-Lantus
GIR AUC0-24 (mg/kg)	74	1470.07 (1256.52, 1683.63)	74	1554.53 (1334.03, 1775.04)	0.95 (0.88, 1.01)	30.1	37.1
GIR AUC0-12† (mg/kg)	74	659.38 (557.84, 760.92)	75	736.31 (625.22, 847.41)	0.90 (0.81, 0.99)	39.5	46.6
GIR AUC12-24 (mg/kg)	74	811.43 (689.89, 932.98)	74	818.20 (700.40, 936.01)	0.99 (0.92, 1.06)	28.1	37.4
GIRmax (mg/kg/min) §	74	2.34 (2.11, 2.57)	74	2.43 (2.18, 2.68)	0.96 (0.91, 1.02)	27.9	33.5

† Number of subjects with at least one administration of the particular treatment (one subject with valid clamp data only out to 18.5 hours after administration of EU-Lantus in one period due to an error in clamping execution. They subsequently discontinued from study participation. Only GIR AUC0-12 calculated from the single period of EU-Lantus administration).
‡ 95% confidence interval for ratio of arithmetic means calculated via Fieller's Theorem
§ Determined from smoothed data

Exploratory comparison of DOA between MK-1293 and EU-approved Lantus did not suggest any meaningful difference in DOA between treatments. The exploratory comparison made using a post hoc survival analysis determined a hazard ratio (MK-1293/EU-approved Lantus) and 95% confidence interval of 1.07 (0.72, 1.59).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Analysis of PK data (and PD data) is acceptable for studies P002 and P005

The PK-studies are in general agreement 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). However, the guideline asks the terminal half-life $T_{1/2}$ of the insulin analogues should be determined where possible. Due to ethical reasons, the sampling period was not optimal and because of that the terminal elimination constants were estimated with extremely high error or even in a few cases could not have been estimated. Given these circumstances, the found differences between MK-1293 and EU-approved Lantus are reasonably similar to each other. Since most of insulin glargine and the M2 metabolite concentrations were, as expected, close to or lower than their LLOQ values, restricting the PK analyses to glargine metabolite M1, the primary active circulating insulin glargine species, is acceptable. The GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) suggest that the lower limit of quantitation (here 100 pg/mL) should be 1/20 of C_{max} (here ~ 400 pg/mL) or lower. However, due to very low plasma concentrations, the deviation from the guideline in this point is considered justified and the analytical methods using a LC-MS/MS assay for analyses of parent glargine, M1 and M2 are acceptable and have been shown to be validated and suitable for the intended purpose. Both studies indicate a somewhat slower rise of M1 glargine metabolite plasma concentration with MK-1293, however, all primary and secondary endpoints for the 90% confidence intervals for a given treatment comparison lie within (0.80, 1.25).

The PK-results from the studies 002 and 005 support bioequivalence between Lantus and MK-1293.

Pharmacodynamics

For long-acting insulins, GIR-$AUC_{(0-T)}$ is the only primary PD endpoint requested by 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). Using $AUC_{(0-T),}$ which corresponds to AUC0-24 for Lantus, rather than $AUC_{(0-t)}$ is recommended by the Guideline and difficulties to determine the duration of action of a long-acting insulin are acknowledged.

The predefined and acceptable comparability margins (0.8; 1.25) were met for the primary endpoints GIR AUC_{0-24}, GIR_{max}, GIR AUC_{12-24} in both studies and for GIR AUC_{0-12} in study 005.

The way of calculating confidence intervals for GIR related metrics was unusual. The Applicant in protocol justified it by stating that in contrast to the PK endpoints which are normally distributed following log transformation, the PD endpoints are normally distributed on the original scale without transformation. It was doubtful that this was valid argument particularly because at planned degree of freedom (larger than 100) it does not really matter what is the distribution of the raw data, the means have normal distribution anyway. The real issue was that some subjects had zero response. It might be argued that these subjects can be considered outliers. The data show that these zero GIR response is not product but patient related. After removing these doubtful data the protocol set criteria was not achieved for the GIR -AUC 0-12h parameter. The assessor does not consider missing the target value as a critical issue because GIR AUC 0-12h is obviously a highly variable (the reference drug within - subject CV equal with 60.2%), absorption process related parameter. In this case widening the acceptance range is allowable.

The minimal deviation of the lower limit of the 95% CI of the Ratio of the Arithmetic Mean of GIR-AUC_{0-12} of 0.91 (0.798, 1.04) in study 002 (MK-1293/EU Lantus) is considered clinically not relevant. In addition, rounding to an

accuracy of two digits after the decimal point (as required for BE studies for generics) would lead to a value of 0.8, which is covered by the predefined acceptance range. The study endpoint was initially defined for the 90% CI [0.91(0.82, 1.02)] in line with FDA requirements and therefore, formally, the predefined study endpoints were reached. In addition, partial AUC values are not required as primary endpoints by the EMA guideline and therefore descriptive analysis would be sufficient.

In patients with T1DM, blood glucose concentrations are typically clamped at 5.6 mmol/L (100 mg/dL; EMEA/CHMP/BMWP/32775/2005_Rev.1). In study 005 the blood sugar level was set to a higher value (130 mg/dL). However evidence from the literature showed that it does not matter whether the clamped glucose level was 100 or 130 mg/dL because in both cases the concentrations fall to the linear uprising part of the glucose concentration - glucose uptake curve, quite far from the saturating concentrations.

The primary objectives of study 005 are not fulfilled completely due to the deviation from the pre-specified analyses of DOA. However, again this value is not required as primary endpoint for Long-acting insulin preparations by the guideline and difficulties for determination are plausible and also addressed in the EMA guideline. In addition, the values from the post hoc analyses did not show evidence for a difference in DOA between Lantus and MK-1293.

Overall, the predefined study objectives appear too ambitious and exceed the requirements of the guideline. The observed study results suggest comparable time-action profiles of MK-1293 and EU-Lantus. Both studies indicate a somewhat slower rise of GIR with MK-1293, however, the difference is small and considered of no clinical relevance.

2.4.5. Conclusions on clinical pharmacology

Study design and analytical methods of the studies 002 and 005 are in acceptable agreement with the relevant EU-guidelines. The PK-results support bioequivalence between Lantus and MK-1293.

The PD-results from the studies 002 and 005 support bioequivalence between Lantus and MK-1293 and are in agreement with the observed pharmacokinetics.

2.4.6. Clinical efficacy

Two phase III studies have been conducted with MK-1293: P003 in subjects with T1DM and P006 in subjects with T2DM. Both studies used EU-approved Lantus. Key goals of these studies were to demonstrate a similar glycemic efficacy with similar insulin doses between MK-1293 and Lantus and to demonstrate safety, with a focus on immunogenicity, between MK-1293 and Lantus treatment groups.

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.

Studies P-003 and P-006

Study design and efficacy endpoints

P003 was a 52-week (phase A 24 weeks and phase B 28 weeks; phase B results were submitted with the responses to the D120 LoQ) multinational, randomized, open-label, 2-parallel group safety and efficacy study comparing MK-1293 and Lantus in subjects with T1DM. Phase A is included in this primary submission and the Phase B data will be submitted after the completion of the additional 28 weeks. Subjects who were ≥18 years of

age with T1DM who at screening were either (1) on any type of intermediate/long-acting subcutaneous insulin (basal insulin) at a total daily dose of ≥10 units/day and using rDNA origin prandial insulin (for ≥4 weeks); or (2) taking pre-mixed insulin with the basal insulin component equivalent to ≥10 units/day, and had a screening A1C ≤11.0% were eligible to participate. Five hundred eight subjects at 84 sites worldwide were randomized to receive either MK-1293 or Lantus in a 1:1 ratio.

P006 was a 24-week multinational, randomized, open-label, parallel group safety and efficacy study comparing MK-1293 and Lantus in subjects with T2DM. Randomization was stratified according to prior insulin status (insulin naïve vs. non-naïve). Subjects who were ≥18 years of age with T2DM who at screening were taking intermediate/long-acting insulin or who required basal insulin for glucose control (based on European Association for the Study of Diabetes guidelines and American Diabetes Association) were eligible to participate. Five hundred thirty-one (531) subjects at 48 sites worldwide were randomized to receive either MK-1293 or Lantus treatment groups in a 1:1 ratio.

In both studies, a screening phase of up to 2 weeks during which subjects continued their current insulin and/or oral anti-hyperglycaemic agent (AHA) treatment (P006 only) was followed by a treatment phase. Subjects received either Lantus or MK-1293 subcutaneously once daily at bedtime. Subjects already taking Lantus once daily at a time other than bedtime were to continue dosing insulin glargine (Lantus or MK-1293) according to the previously established routine. In general, during the study the subjects were to continue dosing insulin glargine at the time established at randomization. Post-randomization, MK-1293 and Lantus doses were individually titrated to the suggested target for fasting fingerstick glucose (FSG) levels of >70 mg/dL (3.9 mmol/L) and ≤100 mg/dL (5.6 mmol/L) using a treat-to-target algorithm. The insulin glargine titration phase began at randomization and continued until there was no required change to the insulin glargine dose for at least 3 contacts in ≥ 2 weeks.

In both P003 and P006, subjects taking prandial insulin were to continue their current prandial insulin regimen, including the use of dose adjustment based on carbohydrate counting and FSG values, during the insulin glargine titration phase. After the insulin glargine titration phase, the prandial insulin was to be adjusted if the investigator determined it was necessary for glucose control. In P006, subjects taking oral AHA treatments were recommended to remain on the doses they were taking prior to screening through the end of the study. A telephone contact was to be performed 14 days after the last dose of study medication to assess for serious adverse events (SAEs).

Analyses of insulin dose (units) and insulin dose per kg body weight (units/kg) at week 24 were based on data in the study medication electronic case report form (eCRF) and included study medication only (bolus insulin was not included in the analysis).

Key **efficacy endpoints** in both studies were:

Primary Endpoint

-Change from baseline in HbA1c at Week 24

Key Secondary Endpoints

-Insulin dose (units) at week 24 and insulin dose per kg of body weight (units/kg) at week 24; study P003 total insulin dose and by component (basal/bolus), study P006 basal insulin dose.

-Change from baseline in fasting plasma glucose (FPG) at week 24.

Key **safety endpoints** were (results are provided in the safety section of this report):

Primary: to assess the effect of treatment with MK-1293 compared with Lantus on anti-insulin antibody development after 24 weeks of treatment. To this end the following parameters were evaluated:

-Anti-insulin-antibodies (AIA): cumulative percentage of subjects with any confirmed positive AIA (including baseline) at any time up through week 24.

-Anti-insulin antibodies (AIA): cumulative percentage of subjects who have negative AIA at baseline but develop confirmed positive AIA at any time up through week 24.

-AIA titers: change from baseline in AIA titers after 24 weeks of treatment.

-Insulin neutralizing antibodies (INAb): proportion of subjects with any post-baseline INAb (based on the subjects who have confirmed positive AIA at the corresponding time point) by baseline immunogenicity status up through 24 weeks of treatment.

Secondary: to assess the safety and tolerability, including body weight, hypoglycaemia and adverse events, of MK-1293 compared to Lantus after 24 and 52 weeks (P-003 only) of treatment.

Subject population studied

MK-1293 was studied in T1DM (study P003) and T2DM (study P006) populations. In both studies, baseline characteristics including age, gender, body mass index (BMI), duration of diabetes, and baseline HbA1c were well balanced between treatment arms. In study P003, 291 (57.3%) of subjects were male, the mean age was 41.7 years and the mean BMI was 26.4 kg/m^2. Subjects had a mean duration of diabetes of 21.8 years and an HbA1c of 8.01%. In study P006, 293 (55.2%) of subjects were male, the mean age was 57.0 years and mean BMI was 32.3 kg/m^2. Subjects had a mean duration of diabetes of 13.4 years and a mean HbA1c of 8.35%. Randomization was stratified by previous insulin use with 161 (30.3%) as insulin naïve and 370 (69.7%) taking insulin at the time of screening.

No imbalances were identified in the percentages of subjects who discontinued the study or in the reasons for discontinuation among the treatment groups within each study and across the studies.

Statistical methods

The primary (non-inferiority) and secondary (equivalence) hypotheses were evaluated by comparing MK-1293 to Lantus on the primary endpoint defined as change from baseline in A1C at Week 24. MK-1293 was to be considered non-inferior to Lantus if the upper bound of the two-sided 95% confidence interval (CI) for the between-treatment difference (MK-1293 minus Lantus) in least-squares (LS) means for the primary endpoint was below 0.4% based on a constrained longitudinal data analysis (cLDA) model. MK-1293 was considered equivalent to Lantus if lower and upper bound of the two-sided 95% CI were between -0.4% and 0.4%.

The cLDA model used to analyze the primary and key secondary endpoints was a repeated measures model that included terms for treatment, prior insulin status (insulin naïve and on insulin), time, the interaction of time by treatment, and the interaction of time by prior insulin status, with a restriction of the same baseline mean across treatment groups.

The FAS population (randomized subjects who received at least one dose of study treatment, and (2) had at least one observation for the analysis endpoint) served as the primary population for the analysis of efficacy data in this study.

A step-down ordered testing procedure was used to control type I error for the primary and secondary hypotheses. The secondary hypothesis of equivalence was only to be tested if the primary hypothesis of non-inferiority was supported. Other efficacy analyses were considered supportive.

The analyses of the proportions of subjects meeting A1C goals of <7.0% and <6.5% at Week 24 were conducted using the Miettinen and Nurminen (M&N) method stratified by prior insulin status.

The cumulative percentage of subjects with any confirmed positive AIA (including baseline) up through Week 24 and the cumulative percentage of subjects who had negative AIA at baseline but developed confirmed positive AIA at any time up through Week 24 were key immunogenicity endpoints of interest. Changes from baseline in AIA titers and the proportion of subjects with any post-baseline INAb by baseline immunogenicity status were also used to assess immunogenicity. Immunogenicity endpoints assessed at Week 24 were primary endpoints of interest for safety. Descriptive summary statistics were provided for these immunogenicity endpoints. No inferential testing was performed.

For all other safety parameters, assessments were performed following a tiered approach by clinical review of all relevant parameters including adverse events, spontaneous reports of local and systemic reactions, PDLCs, laboratory tests, and vital signs. Symptomatic hypoglycemia, injection site reactions (including any reactions recorded as the following MedDRA terms Administration Site Reactions NEC, Infusion Site Reactions, and Application and Instillation Site Reactions), Systemic Allergic Reactions, Anaphylactic Response, and any terms identified by the SMQs: Angioedema SMQ [Narrow], Severe Cutaneous Adverse Reactions SMQ [Broad] after 24 weeks of treatment were pre-specified as events of interest (Tier 1 events). P-values and 95% CIs for between-treatment differences in the percentage of subjects with events for Tier 1 events were calculated using the M&N method.

Results

HbA1c

Efficacy results for HbA1c were similar between MK-1293 and Lantus in studies P003 and P006. Since the upper bound of the confidence interval of the treatment difference was less than the non-inferiority margin of 0.4%, MK-1293 met the pre-specified criterion for non-inferiority to Lantus in reducing HbA1c in both studies. Results are given in the following tables.

Table 1:

P003 (T1DM)
A1C (%): Analysis of Change from Baseline at Week 24 (Constrained Longitudinal Data Analysis)
(FAS)

	Baseline		Week 24		Change from Baseline	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI[1])
MK-1293	241	7.97 (1.16)	219	7.39 (1.09)	241	-0.62 (-0.79, -0.45)
Lantus	258	8.04 (1.25)	236	7.39 (1.16)	258	-0.66 (-0.82, -0.50)
Pairwise Comparison					Difference in LS Means (95% CI)	
MK-1293 vs. Lantus					0.04 (-0.11, 0.19)	
Root Mean Squared Error = 0.92						

[1]Based on cLDA model including terms for treatment, time, prior insulin status (intermediate-acting, or long-acting insulin), and the interaction of time by treatment, and time by prior insulin status.
For Baseline and Week 24, N is the number of subjects with data at the respective time point. For Change from Baseline, N is the number of subjects contributing to the cLDA analysis.
CI= Confidence Interval, LS= Least Squares, SD= Standard Deviation.

Table 2:

P006 (T2DM)

A1C (%): Analysis of Change from Baseline at Week 24 (Constrained Longitudinal Data Analysis)

(FAS)

	Baseline		Week 24		Change from Baseline	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI‡)
MK-1293	263	8.28 (1.30)	241	7.18 (1.01)	263	-1.28 (-1.41, -1.15)
Lantus	263	8.42 (1.25)	245	7.23 (1.02)	263	-1.30 (-1.43, -1.18)
Pairwise Comparison						Difference in LS Means (95% CI)
MK-1293 vs. Lantus						0.03 (-0.12, 0.18)
Root Mean Squared Error = 1.09						

‡Based on cLDA model including terms for treatment, time, prior insulin status (insulin naive, on insulin), and the interaction of time by treatment, and time by prior insulin status.

For Baseline and Week 24, N is the number of subjects with data at the respective time point. For Change from Baseline, N is the number of subjects contributing to the cLDA analysis.

CI= Confidence Interval, LS= Least Squares, SD= Standard Deviation.

A summary of change from baseline in HbA1c for **subpopulations defined by antibody status** is given in the following tables:

Table 3:

Study P003:

A1C (%): Subpopulation Summary of Change from Baseline at Week 24

(FAS/LOCF)

		Baseline	Week 24	Change from Baseline		
Treatment	N	Mean (SD)	Mean (SD)	Mean (SD)	Median	Range
Subpopulation 1†: Subjects who were AIA negative at baseline and were positive at one or more post-baseline time points						
MK-1293	33	8.30 (1.00)	7.72 (0.97)	-0.59 (0.93)	-0.50	-2.8 to 1.1
Lantus	35	8.34 (1.05)	7.51 (1.26)	-0.83 (1.21)	-0.80	-4.3 to 1.3
Subpopulation 2‡: Subjects who were AIA positive at baseline, regardless of their AIA status post-baseline						
MK-1293	133	7.89 (1.15)	7.44 (1.05)	-0.45 (0.72)	-0.30	-2.5 to 1.2
Lantus	151	8.00 (1.28)	7.49 (1.24)	-0.51 (0.93)	-0.50	-3.9 to 4.7
Subpopulation 3: Subjects who were AIA negative at every measurement (baseline and post-baseline).						
MK-1293	70	7.96 (1.24)	7.28 (1.19)	-0.69 (0.96)	-0.55	-4.0 to 1.1
Lantus	64	7.98 (1.32)	7.29 (0.94)	-0.69 (1.03)	-0.55	-3.1 to 1.7
Subpopulation 4: Subjects with positive neutralizing antibodies at any time, among subjects who were AIA positive at any time						
MK-1293	13	7.59 (1.05)	7.23 (1.12)	-0.36 (0.73)	-0.20	-2.4 to 0.4
Lantus	19	8.03 (1.34)	7.52 (0.89)	-0.51 (0.86)	-0.40	-2.7 to 0.7

† 1 subject was included in MK-1293 and 1 in Lantus who were AIA negative at baseline and unconfirmed positive (with no confirmed positive results) at one or more post-baseline time points.

‡ 1 subject was included in MK-1293 and 1 in Lantus who were AIA unconfirmed positive at baseline, regardless of their AIA status post-baseline.

SD = Standard Deviation.

Table 4:

Study P006:

A1C (%): Subpopulation Summary of Change from Baseline at Week 24 or the Last Available Post-baseline Value (FAS with LOCF)

Treatment	N	Baseline Mean (SD)	Week 24 Mean (SD)	Change from Baseline Mean (SD)	Median	Range
Subpopulation 1[†]: Subjects who were AIA negative at baseline and were positive at one or more post-baseline time points						
MK-1293	37	8.45 (1.14)	7.14 (1.03)	-1.31 (1.25)	-1.30	-3.7 to 1.6
Lantus	29	8.84 (1.00)	7.41 (1.16)	-1.43 (1.29)	-1.20	-4.4 to 0.7
Subpopulation 2[‡]: Subjects who were AIA positive at baseline, regardless of their AIA status post-baseline						
MK-1293	49	7.84 (1.25)	7.16 (1.09)	-0.68 (1.05)	-0.30	-3.4 to 0.8
Lantus	41	8.19 (1.08)	7.39 (0.89)	-0.80 (0.93)	-0.70	-3.5 to 1.2
Subpopulation 3: Subjects who were AIA negative at every measurement (baseline and post-baseline).						
MK-1293	168	8.36 (1.31)	7.25 (1.02)	-1.11 (1.18)	-1.00	-4.3 to 2.6
Lantus	177	8.43 (1.30)	7.18 (1.01)	-1.25 (1.10)	-1.10	-4.7 to 1.3
Subpopulation 4: Subjects with positive neutralizing antibodies at any time, among subjects who were AIA positive at any time						
MK-1293	3	8.10 (0.98)	7.10 (1.35)	-1.00 (1.91)	0.00	-3.2 to 0.2
Lantus	1	9.80 (NA)	8.00 (NA)	-1.80 (NA)	-1.80	-1.8 to -1.8

[†]: 1 subject was included in MK-1293 and 3 in Lantus who were AIA negative at baseline and unconfirmed positive (with no confirmed positive results) at one or more post-baseline time points.

[‡]: 2 subjects were included in MK-1293 and 1 in Lantus who were AIA unconfirmed positive at baseline, regardless of their AIA status post-baseline.

SD = Standard deviation.

Insulin dose

MK-1293 and Lantus had numerically similar basal insulin doses at week 24, with a between-treatment group difference in LS means of <2 units (results are given in the tables below). Analyses of total insulin and bolus insulin in study P003 (T1DM) were consistent with the analyses of basal insulin dose (units). In both studies, treatment effects on basal insulin dose (units) and basal insulin dose per kg body weight were also consistent regardless of the AIA status of subjects (for details please refer to Clinical AR).

Table 5:

P003 (T1DM)
Basal Insulin Dose (units): Analysis at Week 24
(Based on the Study Medication eCRF)
(Constrained Longitudinal Data Analysis)
(FAS)

	Day 1		Week 24		Week 24	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI†)
MK-1293	233	28.6 (13.9)	217	32.1 (15.3)	241	36.33 (33.24, 39.42)
Lantus	251	30.4 (17.6)	236	35.4 (21.8)	258	37.07 (34.03, 40.12)
Pairwise Comparison						Difference in LS Means (95% CI)
MK-1293 vs. Lantus						-0.74 (-2.52, 1.04)
Root Mean Squared Error = 18.45						

†Based on cLDA model including terms for treatment, time, prior insulin status (intermediate-acting, or long-acting insulin), and the interaction of time by treatment, and time by prior insulin status.

For Baseline and Week 24, N is the number of subjects with data at the respective time point. For LS mean, N is the number of subjects contributing to the cLDA analysis.

CI= Confidence Interval, LS= Least Squares, SD= Standard Deviation.

Table 6:

P006 (T2DM)
Basal Insulin Dose (units): Analysis at Week 24
(Based on the Study Medication eCRF)
(Constrained Longitudinal Data Analysis)
(FAS)

	Baseline		Week 24		Week 24	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI†)
MK-1293	249	32.7 (26.5)	243	52.7 (32.2)	263	48.22 (44.90, 51.54)
Lantus	249	31.4 (25.2)	247	50.9 (30.5)	262	46.86 (43.54, 50.19)
Pairwise Comparison						Difference in LS Means (95% CI)
MK-1293 vs. Lantus						1.35 (-2.22, 4.93)
Root Mean Squared Error = 29.86						

†Based on a cLDA model including terms for treatment, time, prior insulin status and the interaction of time by treatment, and time by prior insulin status.

For Baseline and Week 24, N is the number of subjects with data at the respective time point. For LS mean, N is the number of subjects contributing to the cLDA analysis.

CI= Confidence Interval, LS= Least Squares, SD= Standard Deviation.

Fasting Plasma Glucose

Clinically meaningful reductions from baseline were observed in both treatment groups in both populations. In T1DM (study P003) after 24 weeks of treatment, the FPG reduction from baseline was numerically greater with Lantus compared to MK-1293 (-16.8mg/dl for MK-1293 and -26.4 mg/dl for Lantus). In study P006, the reduction in FPG from baseline to week 24 was similar between MK-1293 (-35.0 mg/dl) and Lantus (-38.4mg/dl). Results are given in the following table:

Table 7:

P003 (T1DM)
Fasting Plasma Glucose (mg/dL): Analysis of Change from Baseline at Week 24
(Constrained Longitudinal Data Analysis)
(FAS)

	Baseline		Week 24		Change from Baseline	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI[‡])
MK-1293	240	167.8 (78.4)	219	155.5 (74.4)	241	-16.8 (-33.4, -0.2)
Lantus	258	166.8 (78.8)	235	146.0 (66.1)	258	-26.4 (-42.5, -10.3)
Pairwise Comparison					Difference in LS Means (95% CI)	
MK-1293 vs. Lantus					9.6 (-3.0, 22.2)	
Root Mean Squared Error = 92.82						

[‡]Based on cLDA model including terms for treatment, time, prior insulin status (intermediate-acting, or long-acting insulin), and the interaction of time by treatment, and time by prior insulin status.
For Baseline and Week 24, N is the number of subjects with data at the respective time point. For Change from Baseline, N is the number of subjects contributing to the cLDA analysis.
CI= Confidence Interval, LS= Least Squares, SD= Standard Deviation.

Table 8:

P006 (T2DM)
Fasting Plasma Glucose (mg/dL): Analysis of Change from Baseline at Week 24
(Constrained Longitudinal Data Analysis)
(FAS)

	Baseline		Week 24		Change from Baseline	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI[‡])
MK-1293	263	153.7 (48.4)	241	123.0 (45.4)	263	-35.0 (-41.3, -28.6)
Lantus	263	151.8 (50.4)	245	119.7 (37.3)	263	-38.4 (-44.8, -32.1)
Pairwise Comparison					Difference in LS Means (95% CI)	
MK-1293 vs. Lantus					3.5 (-3.7, 10.7)	
Root Mean Squared Error = 55.05						

[‡]Based on cLDA model including terms for treatment, time, prior insulin status (insulin naive, on insulin), and the interaction of time by treatment, and time by prior insulin status.
For Baseline and Week 24, N is the number of subjects with data at the respective time point. For Change from Baseline, N is the number of subjects contributing to the cLDA analysis.
CI= Confidence Interval, LS= Least Squares, SD= Standard Deviation.

HbA1c goals

In P003 (T1DM), the proportions of subjects with HbA1c below 7.0% and below 6.5% at week 24 were similar in the MK-1293 and Lantus treatment groups. The proportion of subjects withHbA1c <7.0% was 37.0% and 37.7% in the MK-1293 and Lantus groups. The proportion of subjects with HbA1c <6.5% was 20.5% and 21.6% in the MK-1293 and Lantus groups, respectively.

In P006 (T2DM) the proportions of subjects with HbA1c below 7.0% and below 6.5%, respectively, at week 24 were similar in the MK-1293 and Lantus treatment groups. The proportion of subjects with HbA1c <7.0% was 46.5% and 43.7% in the MK-1293 and Lantus groups, respectively. The proportion of subjects with HbA1c <6.5% was 21.6% and 22.4% in the MK-1293 and Lantus groups, respectively.

Results of Phase B of study P003 (52 week data)

The efficacy and safety of MK-1293 compared to Lantus after 52 weeks of treatment were key secondary objectives of study P003. Clinically meaningful reductions in A1C at Week 52 were sustained in both MK-1293 and Lantus groups. The LS mean change from baseline (95% CI) in the MK-1293 group was -0.35% (-0.53, -0.17) from a mean baseline A1C of 7.97%; for the Lantus group, the LS mean change from baseline (95% CI) was -0.33% (-0.05, -0.16) from a mean baseline A1C of 8.03%. The between-group difference (MK-1293 minus Lantus) in LS mean change from baseline in A1C was -0.02% with a 95% CI of (-0.18, 0.14). Similar effects were found on FPG, total, basal, and bolus insulin dose per kg body weight after 52 weeks of treatment (see table below).

Results for Key Efficacy Endpoints at Week 52 (FAS)

Treatment	N	LS Mean (95% CI)	Difference in LS Means vs. Lantus (95% CI)
A1C (%) Change from Baseline at Week 52			
MK-1293	241	-0.35 (-0.53, -0.17)	-0.02 (-0.18, 0.14)
Lantus	258	-0.33 (-0.50, -0.16)	
FPG (mg/dL) Change from Baseline at Week 52			
MK-1293	241	-17.9 (-35.8, 0.1)	-5.4 (-19.7, 8.9)
Lantus	258	-12.5 (-29.9, 4.9)	
Total Insulin dose (units) at Week 52			
MK-1293	228	59.16 (53.97, 64.34)	-1.77 (-4.92, 1.39)
Lantus	240	60.93 (55.79, 66.06)	
Basal Insulin dose (units) at Week 52			
MK-1293	241	36.08 (33.14, 39.03)	-0.42 (-2.33, 1.48)
Lantus	258	36.51 (33.63, 39.39)	
Bolus Insulin dose (units) at Week 52			
MK-1293	228	22.15 (19.03, 25.27)	-1.50 (-3.69, 0.69)
Lantus	240	23.65 (20.57, 26.73)	
Total Insulin dose per body weight (units/kg) at Week 52			
MK-1293	228	0.75 (0.70, 0.81)	-0.02 (-0.05, 0.02)
Lantus	240	0.77 (0.71, 0.82)	
Basal Insulin dose per body weight (units/kg) at Week 52			
MK-1293	241	0.46 (0.43, 0.50)	-0.00 (-0.02, 0.02)
Lantus	258	0.47 (0.43, 0.50)	
Bolus Insulin dose per body weight (units/kg) at Week 52			
MK-1293	228	0.28 (0.24, 0.31)	-0.02 (-0.04, 0.01)
Lantus	240	0.30 (0.26, 0.33)	

Based on a cLDA model including terms for treatment, time, prior insulin status (intermediate-acting, or long-acting insulin), and the interaction of time by treatment, and time by prior insulin status.
A1C = Hemoglobin A1C, CI = Confidence Interval, FPG = Fasting Plasma Glucose, LS = Least Squares.

2.4.7. Discussion on clinical efficacy

Design and conduct of clinical studies

The main focus of this application is to show that MK-1293 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 too insensitive to detect potential, clinically relevant differences and can therefore only be considered supportive. No dose-finding studies have been performed which is acceptable for a biosimilar.

The efficacy profile of MK-1293 was demonstrated based on 24-week data from two phase III clinical trials, one in subjects with T1DM (P003) and one in subjects with T2DM (P006). Both studies were multinational, randomized, open-label, 2-parallel group efficacy studies comparing MK-1293 and Lantus in subjects with T1DM and T2DM, respectively.

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 insulin doses, the proportion of subjects achieving glycaemic goals and fasting plasma glucose (FPG) are commonplace in studies of anti-hyperglycaemic medications.

Both studies were 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.

Efficacy data

In both studies, the treatment groups were generally well-balanced and representative of the EU population. Equivalence was demonstrated between MK-1293 and Lantus for change from baseline in HbA1c at 24 weeks in both T1DM and T2DM subjects. Generally similar changes from baseline were observed between MK-1293 and Lantus in other parameters of efficacy including insulin dose and insulin dose/kg, 7-point SMBG measurements, and patients with HbA1c at goal.

In P003 (T1DM), after 24 weeks of treatment, a numerically greater reduction in FPG was observed with Lantus than with MK-1293 (with the 95% CI around the between-group difference including 0). However, in P006 (T2DM), no notable difference in FPG reduction was seen. Given the comparability of HbA1c, insulin dose, and 7-point SMBG seen in both studies, the numerical difference in FPG in P003 is probably a result of normal variability and unlikely clinically meaningful.

In both treatment groups, maximal A1C-lowering was seen at Week 24. Between Week 24 and Week 52, the reduction from baseline in A1C diminished modestly, and by a similar amount in both groups. Therefore, it may best be explained by less compliance to diet and exercise.

In both studies, change from baseline in HbA1c was similar between MK-1293 and Lantus in subjects regardless of AIA status. Change from baseline HbA1c was also similar in subpopulations based on baseline characteristics including age, gender, race, baseline BMI, baseline HbA1c, duration of diabetes and prior insulin use. In P003 (T1DM) a lower reduction in A1C was noted with MK-1293 vs. Lantus in the subgroup of subjects from the geographic region of Australia- New Zealand- South Africa and a higher reduction in HbA1c was noted with MK-1293 vs. Lantus in the subgroup of subjects from the geographic region of Latin America. This pattern of differences was not seen in study P006, and the relatively small group sizes in these regions do not allow for drawing valid conclusions.

2.4.8. Conclusions 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, studies P-003 and P-006 are considered only supportive with regard to efficacy in this application dossier. Equivalence with regard to Hb1c change from baseline at Week 24 between MK-1293 and Lantus in both T1DM (P003) and T2DM (P006) subjects was demonstrated and this was achieved at similar Week 24 insulin doses. The results on the secondary endpoints generally support the primary outcome. These data are consistent with the Phase I results demonstrating PD and PK similarity between MK-1293 and Lantus. These data support the conclusion that the efficacy profile of MK1293 is similar to that of Lantus.

Albeit glycaemic control diminished during the long-term extension period in study P003, the extent was comparable between Lantus and MK-1293 and therefore, the attenuation of glycaemic control does not alter the conclusion of similar efficacy between MK-1293 and Lantus.

2.5. Clinical safety

The main focus of the safety assessment in a biosimilar application lies on immunogenicity. Therefore, mainly the phase 3 studies (P003 in T1DM and P006 in T2DM) will be discussed here. From the short-term studies no relevant safety information can be derived with the following exception: In Study P002, a trend of higher AE incidence in MK-1293 group could be seen for overall AE incidence and for General disorders and administration site conditions SOC. Injection site pain (8 vs. 2) and vessel puncture pain (3 vs. 0) occurred with a higher frequency in MK-1293 group than in EU-Lantus group. Quality related background cannot be excluded.

Patient exposure

In phase 3, 241 subjects with T1DM and 263 subjects with T2DM received treatment with MK-1293, while 258 subjects with T1DM and 263 subjects with T2DM received treatment with EU-approved Lantus. In subjects with T1DM or T2DM, the mean duration of exposure to MK-1293 was comparable to the mean duration of exposure to Lantus (160 to 163 days across studies and treatment groups).

Adverse events

In the T1DM population (Study P003), at least one adverse event was reported in 216 of the 241 subjects (89.6%) in the MK-1293 group and 232 of 258 subjects (89.9%) in the Lantus group (see tables below). In theT2DM population (Study P006), at least one adverse event was reported in 206 of the 263 subjects (78.3%) in the MK-1293 group and 188 of 263 subjects (71.5%) in the Lantus group. The overall incidence of adverse events, as well as the incidence in specific adverse event summary categories, was similar for the two treatment groups in both patient populations. In Type 2 diabetics (Study P006) there was a numerical imbalance in serious AEs disfavouring MK-1293 (13 vs. 9 patients, 4.9% vs. 3.4%). However, the events were scattered across SOCs (e.g., two events were chest pain) and showed no notable pattern so that no specific concerns regarding MK-1293 became obvious. Serious AEs and deaths are further discussed in the respective section below.

Table 9: PD003 (T1DM): Analysis of Adverse Events Summary (ASaT); 52 wk

	MK-1293 n (%)	Lantus n (%)	Difference in % vs. Lantus Estimate (95% CI)
Subjects in population	241	258	
with one or more adverse event	**216 (89.6)**	**232 (89.9)**	-0.3 (-5.8, 5.1)
with no adverse event	25 (10.4)	26 (10.1)	0.3 (-5.1, 5.8)
with drug-related‡ adverse event	116 (48.1)	137 (53.1)	-5.0 (-13.7, 3.8)
with serious adverse event	**23 (9.5)**	**30 (11.6)**	-2.1 (-7.6, 3.4)
with serious drug-related adverse event	7 (2.9)	11 (4.3)	-1.4 (-4.9, 2.1)
who died	0 (0.0)	0 (0.0)	
discontinued§ due to an adverse event	2 (0.8)	6 (2.3)	-1.5 (-4.3, 0.9)
discontinued due to a drug-related adverse event	1 (0.4)	0 (0.0)	
discontinued due to a serious adverse event	1 (0.4)	3 (1.2)	
discontinued due to a serious drug-related adverse event	0 (0.0)	0 (0.0)	

Table 10: P006 (T2DM): Analysis of Adverse Events Summary (ASaT)

	MK-1293 n (%)	Lantus n (%)	Difference in % vs. Lantus Estimate (95% CI)
Subjects in population	263	263	
with one or more adverse event	**206 (78.3)**	**188 (71.5)**	**6.8 (-0.6, 14.2)**
with no adverse event	57 (21.7)	75 (28.5)	-6.8 (-14.2, 0.6)
with drug-related‡ adverse event	99 (37.6)	99 (37.6)	0.0 (-8.3, 8.3)
with serious adverse event	**13 (4.9)**	**9 (3.4)**	**1.5 (-2.0, 5.3)**
with serious drug-related adverse event	1 (0.4)	0 (0.0)	
who died	1 (0.4)	1 (0.4)	
discontinued§ due to an adverse event	1 (0.4)	3 (1.1)	
discontinued due to a drug-related adverse event	0 (0.0)	1 (0.4)	
discontinued due to a serious drug-related adverse event	1 (0.4)	2 (0.8)	
discontinued due to a serious adverse event	0 (0.0)	0 (0.0)	

§Study medication withdrawn.
‡ Determined by the investigator to be related to the drug.
CI = Confidence Interval.

The incidences of specific **drug-related** (as considered by the investigator) adverse events were similar between the two treatment groups, with a low frequency of events (<2%) across all specific adverse events other than the adverse event of hypoglycaemia, which occurred in 45.6% of subjects in the MK-1293 group and 50.4% in the Lantus group in T1DM. For T2DM, the incidence of hypoglycaemia events considered related was 35.0 vs. 35.4% (MK-1293 vs. Lantus).

Taken together, the AE listings shown above give no hint that the safety and tolerability of MK-1293 could be inferior to that of Lantus except for a small difference in injection site reactions. The numerical differences observed in some categories are most likely due to random fluctuation since no pattern indicative for an underlying mechanism was observed.

AE of special interest: Hypoglycaemia

All events of fingerstick glucose (FSG) <70 mg/dL were automatically transferred from the subjects' glucose meters to the eDiary via Bluetooth connection. Subjects also were to report in the eDiary events of symptomatic

hypoglycaemia whether or not confirmatory blood glucose measurements were obtained. In addition, events that were not reported in the eDiary but were documented in the clinic notes were also entered into the database by investigators. Symptomatic events assessed as likely to be hypoglycaemia were to be reported by investigators as adverse events of hypoglycaemia; a concurrent glucose measurement was not required. However, subjects were counselled to obtain FSG values if possible, when symptoms of hypoglycaemia occurred. Asymptomatic events were defined as episodes without symptoms of hypoglycaemia, but with a glucose level ≤70 mg/dL (≤3.9 mmol/L). Asymptomatic events could also be reported as adverse events at the discretion of the investigator.

The MK-1293 and Lantus groups were similar in the T1DM and the T2DM study with regard to the incidence of hypoglycaemia adverse events including those that were severe (i.e., defined as requiring medical or nonmedical assistance regardless of whether the subject received assistance). Incidences of the various categories of hypoglycaemia were well balanced between treatment groups in Study P006 (see the following two tables for details).

Table 11: Study P003 (T1DM): Analysis of Subjects with Hypoglycemia Adverse Events (ASaT); 52 wk

	MK-1293 n (%)	Lantus n (%)	Difference in % vs. Lantus Estimate (95% CI†)
Subjects in population	241	258	
With one or more:			
Adverse event(s) of hypoglycemia	185 (76.8)	205 (79.5)	-2.7 (-10.0, 4.6)
Symptomatic	184 (76.3)	204 (79.1)	-2.7 (-10.1, 4.6)
Severe	54 (22.4)	63 (24.4)	-2.0 (-9.4, 5.5)
Requiring non-medical assistance	39 (16.2)	41 (15.9)	0.3 (-6.2, 6.8)
Requiring medical assistance	25 (10.4)	31 (12.0)	-1.6 (-7.3, 4.0)
Asymptomatic	41 (17.0)	47 (18.2)	-1.2 (-7.9, 5.6)
Unknown Symptoms	8 (3.3)	5 (1.9)	1.4 (-1.6, 4.7)

Table 11: Study P006 (T2DM): Analysis of Subjects with Hypoglycemia Adverse Events (ASaT)

	MK-1293 n (%)	Lantus n (%)	Difference in % vs. Lantus Estimate (95% CI†)
Subjects in population	263	263	
With one or more:			
Adverse event(s) of hypoglycemia	142 (54.0)	142 (54.0)	0.0 (-8.5, 8.5)
Symptomatic	140 (53.2)	137 (52.1)	1.1 (-7.4, 9.6)
Severe	24 (9.1)	22 (8.4)	0.8 (-4.2, 5.7)
Requiring non-medical assistance	22 (8.4)	20 (7.6)	0.8 (-4.0, 5.6)
Requiring medical assistance	2 (0.8)	3 (1.1)	
Asymptomatic	18 (6.8)	18 (6.8)	0.0 (-4.5, 4.5)
Unknown Symptoms	4 (1.5)	1 (0.4)	1.1 (-0.7, 3.5)

†Based on Miettinen & Nurminen method. The 95% CI was computed only for those endpoints with at least 4 subjects having events in one or more treatment groups.
Subjects are counted a single time for each applicable category.
Symptomatic episode: Episode with clinical symptoms attributed to hypoglycemia, without regard to biochemical documentation.
Asymptomatic episode: Episode without symptoms attributed to hypoglycemia, but with a glucose level ≤70 mg/dL or ≤3.9mmol/L
Severe episode: Episode that required assistance, either medical or non-medical. Episodes with a markedly depressed level of consciousness, a loss of consciousness, or seizure were classified as having required medical assistance, whether or not medical assistance was obtained
"Unknown symptoms" refers to events which could not be classified as symptomatic or asymptomatic due to incomplete information. CI = Confidence Interval.

Also, no relevant differences between MK-1293 and Lantus were observed when other categories of hypoglycaemia were considered such as subjects with lowest blood glucose below 70 mg/dl vs. below 50 mg/dl or the number of hypoglycaemic episodes.

There was a numerical imbalance in severe hypoglycaemias disfavouring MK-1293; the Applicant explained that this was driven by 2 patients with repeated hypoglycaemias. It is known that some patients can have difficulties to stabilise their blood glucose level for various reasons. Since only two patients in the MK-1293 group were affected, it is unlikely that this was related to the MK-1293 product.

Serious adverse events and deaths

Serious AEs

Study 003 (T1DM): The incidence of serious adverse events was similar in the two treatment groups, with the serious adverse event of hypoglycaemia the most common, reported in 5 subjects in each group, with 3 subjects in the MK-1293 group having other hypoglycaemic-related events (serious adverse events of hypoglycaemic seizure in 2 subjects and hypoglycaemic unconsciousness in 1 subject) and 2 subjects in the Lantus group having other hypoglycaemia-related events (serious adverse events of hypoglycaemic seizure in 1 subject and hypoglycaemic unconsciousness in 1 subject). Two subjects in the MK-1293 group experienced a serious adverse event of pneumonia.

There were 7 subjects in the MK-1293 group who experienced 9 drug-related serious adverse events. All of these events were hypoglycaemia-related and are discussed in the respective section below.

Study 006 (T2DM): In the MK-1293 treatment group, the only specific serious adverse event term reported in more than one subject was non-cardiac chest pain, which was reported for 2 subjects. Overall, serious adverse events were scattered across SOCs, showing no notable pattern, with no meaningful differences between the treatment groups.

One subject in the MK-1293 group experienced a serious adverse event (hypoglycaemia) that was considered to be drug-related by the investigator.

Deaths

There were no deaths in the T1DM study P003. In P006 (T2DM) one subject in the MK-1293 group died of a road traffic accident and one subject in the Lantus group died of congestive heart failure. Neither of the adverse events resulting in death was considered by the investigator to be related to study medication or to study procedure, nor was there any indication that either event was related to hypoglycaemia.

Taken together, the analysis of SAEs and deaths yielded no safety signals for MK-1293.

Laboratory findings

Laboratory findings did not reveal meaningful differences between MK-1293 and Lantus. Blood glucose levels are discussed in the section on hypoglycaemia (AE of special interest) above.

Safety in special populations

Special populations are not relevant for a biosimilar application. Therefore, no special safety analyses in these populations were provided.

Immunological events

Immunogenicity of MK-1293 compared to Lantus will be addressed at three levels. First, formation of binding and neutralising antibodies against insulin glargine; second, compilation of potential hypersensitivity reactions; and third, clinical signs of neutralising antibodies (i.e. increased insulin need or worsening glycaemic control).

Anti-insulin antibodies

Methods: Serum samples were collected for anti-insulin antibodies (AIA) at Day 1, Week 12, and Week 24. Samples found to screen and confirm positive in the AIA assays for screening and specificity, respectively, were to be assessed in the titre assay. The endpoint titre for the sample was defined as the reciprocal of the dilution that generates a mean instrument response greater than the cut point of the plate, where the subsequent dilution in the series results in a mean signal less than or equal to the plate cut point. Samples that confirmed positive for AIA were also to be tested for the ability to neutralise the action of glargine in a cell–based assay (neutralising antibodies, NAb).

Detection of anti-insulin antibodies (AIA) was performed by a 3-tiered assay approach that consists of: (1) a screening assay (Tier 1) for the detection of potential anti-insulin antibody (AIA) positive samples at a 95% confidence level, (2) a confirmatory assay (Tier 2) to confirm if these potential positive samples are true AIA positive with 99% confidence level, and (3) an antibody titre assessment (Tier 3) to determine the titer of AIA confirmed samples. All three tiers of the assays were developed and validated in healthy subjects and subjects with T1DM and T2DM. To further characterize AIA-positive samples, a NAb assay was also developed and validated to assess the ability of confirmed AIA positive samples from Tier 2 to neutralize the functional activity of insulin glargine.

The screening and confirmatory AIA assays (Tier 1 and Tier 2) utilized a standard bridging electrochemiluminescence (ECL) immunoassay on the Meso Scale Discovery (MSD) platform. Prior to analysis, serum samples were treated with acid to dissociate the insulin-AIA complex and with charcoal to remove insulin without removing potentially present AIAs to minimize competition of AIA binding to unlabelled insulin. This assay uses MK-1293 labelled with Biotin (as capture reagent) and MK-1293 labelled with ruthenium (as detection regent) to bridge and detect AIA against either MK-1293 or Lantus. Comprehensive method validation was conducted using a polyclonal affinity purified guinea pig anti-Lantus antibody positive control. Validation results confirmed the suitability of the assays for the intended use. Based on analytical similarities between Lantus and MK-1293 and the performance similarities of these two AIAs in the assay, the use of a single AIA assay utilizing an anti-Lantus AIA positive control is acceptable.

Neutralising capacity was determined in HepG2 hepatoma cells which express a high number of insulin receptors (IR). The capacity of the antibodies to neutralise glargine-induced insulin receptor phosphorylation in these cells was measured. IR phosphorylation was determined by an anti-phosphotyrosine antibody labelled with a Sulfo-Tag reagent, leading to an increase in the ECL signal. The presence of NAb neutralises the biological activity of MK-1293 or Lantus and thus reduces ligand induced phosphorylation of IR and the ECL signal. The positive controls used for validation were Guinea pig polyclonal anti-Lantus and anti-MK-1293 antibody. Validation results confirmed the suitability of the assay. MK-1293 and Lantus performed similarly in the cell-based Nab assay, and the anti-Lantus antibody positive control neutralised both MK-1293 and Lantus similarly. This supports the use of one Nab assay to assess AIA in both Lantus and MK-1293 treated subjects.

Percentage of AIA-positive patients: Immunogenicity was analysed by in T1DM patients obtaining the numbers and percentages of subjects who were AIA positive at baseline, at any time up to Week 12, 24, 36 and 52 (always including baseline) among the entire ASaT population, as well as the numbers and percentages of

baseline-negative subjects who became positive post-baseline. The treatment groups were similar for all of these time points; in most cases AIA incidence was slightly lower with MK1293 than with Lantus. See table below for details.

Table 12: Study P003 (T1DM): Analysis of the Cumulative Percentage of Subjects with Positive AIA up through Week 52 (ASaT)

	MK-1293 n/m (%)	Lantus n/m (%)	MK-1293 vs. Lantus Difference in % (95% CI)§
Subjects in Population	241	258	
AIA positive at Baseline†	134/237 (56.5)	152/253 (60.1)	-3.5 (-12.2, 5.2)
AIA positive at or before Week 12 (including Baseline)‡	158/239 (66.1)	179/257 (69.6)	-3.5 (-11.8, 4.7)
AIA positive at or before Week 24 (including Baseline)††	169/241 (70.1)	191/258 (74.0)	-3.9 (-11.8, 4.0)
AIA positive at or before Week 36 (including Baseline)	173/241 (71.8)	193/258 (74.8)	-3.0 (-10.8, 4.7)
AIA positive at or before Week 52 (including Baseline)‡	177/241 (73.4)	195/258 (75.6)	-2.1 (-9.8, 5.5)
Subjects AIA negative at Baseline			
Subjects in Population	103	101	
AIA positive after Baseline and at or before Week 12	23/99 (23.2)	25/96 (26.0)	-2.8 (-15.0, 9.3)
AIA positive after Baseline and at or before Week 24	33/101 (32.7)	35/98 (35.7)	-3.0 (-16.1, 10.1)
AIA positive at or before Week 36 (including Baseline)	37/101 (36.6)	37/98 (37.8)	-1.1 (-14.5, 12.3)
AIA positive at or before Week 52 (including Baseline)‡	41/101 (40.6)	39/98 (39.8)	0.8 (-12.8, 14.3)

In Type 2 diabetics, antibody formation was followed up to Week 24, according to the study duration. No relevant differences between the treatment groups became obvious; for details see table below.

Table 13: Study P006 (T2DM): Analysis of the Cumulative Percentage of Subjects with Positive AIA (ASaT)

	MK-1293 n/m (%)	Lantus n/m (%)	MK-1293 vs. Lantus Difference in % (95% CI)§
All Subjects			
Subjects in Population	263	263	
AIA positive at Baseline†	49/248 (19.8)	41/245 (16.7)	3.0 (-3.8, 9.9)
AIA positive at or before Week 12 (including Baseline)‡	70/253 (27.7)	68/252 (27.0)	0.7 (-7.1, 8.5)
AIA positive at or before Week 24 (including Baseline)††	91/262 (34.7)	76/262 (29.0)	5.7 (-2.3, 13.7)
Subjects AIA negative at Baseline			
Subjects in Population	199	203	
AIA positive after Baseline and at or before Week 12	19/191 (9.9)	24/193 (12.4)	-2.5 (-9.0, 3.9)
AIA positive after Baseline and at or before Week 24	37/192 (19.3)	29/195 (14.9)	4.4 (-3.1, 12.0)
m = number of subjects with AIA results for the respective time period. n = number of subjects with one or more AIA positive results (confirmed or unconfirmed) for the respective time period.			

[§]Calculated via Miettinen & Nurminen method.
[†] 2 subjects were included in MK-1293 and 1 in Lantus who were AIA unconfirmed positive at Baseline.
[‡] 2 subjects were included in MK-1293 and 2 in Lantus who were AIA unconfirmed positive (with no confirmed positive results) at or before Week 12.
[††] 3 subjects were included in MK-1293 and 3 in Lantus who were AIA unconfirmed positive (with no confirmed positive results) at or before Week 24.

Among subjects who were negative at baseline but became positive during the study, subgroup analyses for occurrence of positive AIAs were conducted for subgroups of subjects defined by prior insulin status (naïve and on insulin), gender, age (tertiles) and region. Results were generally consistent across the subgroups, although the sample sizes in some subgroups were too small to draw meaningful conclusions.

Antibody titres: In general, there was little difference in titre between groups at baseline and 12 Weeks in both populations, for the T1DM patients (Study P003) as well as for the T2DM patients (P006); for details see the following two tables. In Study P006 at Weeks 12 and 24, there was a numerically higher mean antibody titre in the MK-1293 group than in the Lantus group. Accordingly, the mean change from baseline was numerically higher in the MK-1293 group. A higher mean titer observed in the MK-1293 group (21.2) compared to the Lantus group (5.1) at Week 24 was driven by one subject. This individual was AIA negative at baseline and Week 12 and AIA positive (titer 3125), NAb-negative at Week 24. This high titer was not associated with any adverse events. However, since the effect was not observed in the (in respect to immunogenicity) more sensitive T1DM study, it is not considered clinically relevant.

Table 14: P003 (T1DM): Summary of Change from Baseline in AIA Titers Over Time (Week 0-52) (ASaT)

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline Mean (SD)	Median	Range
Baseline						
MK-1293	222	6.7 (19.2)				
Lantus	235	9.3 (44.5)				
Week 12						
MK-1293	196	6.2 (17.8)	5.9 (19.3)	-0.8 (13.6)	0.0	-124.0 to 120.0
Lantus	216	9.6 (45.6)	12.6 (60.5)	0.7 (20.5)	0.0	-100.0 to 124.0
Week 24						
MK-1293	186	6.1 (18.3)	6.6 (19.8)	-0.1 (17.5)	0.0	-100.0 to 124.0
Lantus	199	9.5 (46.2)	13.0 (63.2)	0.2 (23.2)	0.0	-120.0 to 124.0
Week 36						
MK-1293	173	5.9 (16.8)	6.8 (20.3)	-0.3 (13.4)	0.0	-100.0 to 120.0
Lantus	200	9.6 (46.9)	12.2 (61.5)	0.1 (20.4)	0.0	-124.0 to 120.0
Week 52						
MK-1293	164	5.2 (14.4)	4.4 (13.7)	-1.6 (9.9)	0.0	-100.0 to 24.0
Lantus	177	9.7 (47.9)	13.0 (65.6)	0.1 (20.3)	0.0	-120.0 to 100.0

SD = Standard Deviation.
N = number of subjects with AIA results at the respective time point .

Table 15: P006 (T2DM): Summary of Change from Baseline in AIA Titres at Week 12 and 24 (ASaT)

Treatment	N	Baseline Mean (SD)	Time Point Mean (SD)	Change from Baseline Mean (SD)	Median	Range
Baseline						
MK-1293	238	5.6 (42.1)				
Lantus	238	6.1 (42.2)				
Week 12						
MK-1293	220	5.2 (42.4)	8.9 (45.9)	2.3 (18.4)	0.0	-100.0 to 124.0
Lantus	219	6.4 (43.5)	4.8 (18.4)	-1.5 (46.0)	0.0	-600.0 to 124.0
Week 24						
MK-1293	197	6.0 (44.7)	21.2 (212.7)	19.9 (223.3)	0.0	-100.0 to 3124.0
Lantus	208	6.0 (43.4)	5.1 (18.7)	1.5 (18.1)	0.0	-124.0 to 124.0

SD = Standard Deviation.
N = number of subjects with AIA results at the respective time point.

Neutralising antibodies: Overall, the incidence of neutralising antibodies was low. In study **P003**, 13 subjects in the MK-1293 group and 20 subjects in the Lantus group had neutralising antibodies post-baseline. For further details see the table below. No relevant differences between MK-1293 and Lantus were detected. In **P006** only 3 subjects, 1 in the Lantus group who was AIA negative at baseline and 2 in the MK-1293 group who were AIA positive/neutralising antibody negative at baseline, developed neutralising antibodies post-baseline.

Table 16: P003 (T1DM): Summary of Post-baseline Neutralising Antibody Status by Baseline Immunogenicity Status up through Week 52 (ASaT)

	MK-1293		Lantus	
	N	n (%)	N	n (%)
Baseline immunogenicity status				
AIA Negative	103	3 (2.9)	101	0 (0.0)
AIA Positive, neutralizing antibody negative	129	8 (6.2)	145	17 (11.7)
AIA Positive, neutralizing antibody positive	4	2 (50.0)	6	3 (50.0)

N= number of subjects in the baseline category.
n= number of subjects who are neutralizing antibody positive at any time post-baseline.

Table 17: P006 (T2DM): Summary of Post-baseline Neutralising Antibody Status by Baseline Immunogenicity Status (ASaT)

	MK-1293		Lantus	
	N	n (%)	N	n (%)
Baseline immunogenicity status				
AIA negative	199	0 (0.0)	204	1 (0.5)
AIA positive, neutralizing antibody negative	46	2 (4.3)	40	0 (0.0)
AIA positive, neutralizing antibody positive	1	0 (0.0)	0	0 (0.0)

N= number of subjects in the baseline category.
n= number of subjects who are neutralizing antibody positive at any time post-baseline.

Potential hypersensitivity reactions

Potential hypersensitivity reactions (consisting of injection site reactions, anaphylactic responses, angioedema and severe cutaneous adverse reactions) were infrequent. They were considered not related to study drug by the investigator and there were no relevant differences between the MK-1293 and the Lantus groups.

Clinical signs indicative for neutralising antibodies

Neutralising antibodies in the plasma of the study participants were sought with an in-vitro assay (see above). However, it is not known whether this assay is sensitive enough to detect all neutralising antibodies. Vice versa, the in-vitro assay may detect antibodies which in fact do not have clinical consequences. Therefore, clinical signs can help identifying clinically relevant antibody formation. Neutralising the action of insulin in vivo by antibodies is expected to lead to worsening glycaemic control and in turn, to counteract it, to higher insulin need. The Applicant has provided the time course of mean daily insulin need. In both phase 3 studies, P003 and P006, there were no signs for increased mean insulin need in the MK-1293 groups as compared to the Lantus groups.

As absence of a difference in mean insulin need and glycaemic control does not rule out formation of clinically relevant antibodies in a small number of patients, the Applicant provided scatter plots which visualise the correlation between insulin need, glycaemic control (HbA1c) and antibody titre for each individual patient. Three patients in total had poor glycaemic control accompanied by high antibody titre at least at one time point, but the poor glycaemic control could be explained otherwise. Thus, there was no hint for clinically meaningful neutralising antibody formation.

Safety related to drug-drug interactions and other interactions

This aspect is not relevant for a biosimilar application and was therefore not studied.

Discontinuation due to AEs

See section on adverse events above.

Safety aspects related to the injection device (pen)

EU Human Factors Evaluation Summary Report (dated25 Jun 2015)

A new disposable multiple dose pen injector has been developed to deliver a new insulin glargine product to patients with type 1 and type 2 diabetes mellitus. The intended use is self-administration of a subcutaneous injection. In line with the requirements of Council Directive 93/42/EEC and the FDA Guidelines ("Applying human factors and usability engineering to optimize medical device design" and "Incorporating human Factors engineering into risk management") information was given on the intended use of the product, users, use environment, and performing task analysis, and the use error analysis (performed by leveraging the public safety data from similar competitors' products). A Summative Design Validation Study was performed in the EU including 38 participants (also representing pen inexperienced patients and healthy control persons).

As an overall result, the pen injector was found to be a product with moderate risk. Some use errors were found that could cause consequences that require medical intervention (e. g. dialling the incorrect test dose, underdosing due to failure of patients to wait for 10 sec after injection, insulin mix-up). All mitigations identified during the use error analysis became design requirements or inputs into packaging and label design. All risks associated with potential use errors fall into the "low" to "as low as reasonably practicable" (ALARP) range and

all risks are considered acceptable and controlled as far as possible according to the device risk management plan.

In conclusion, the Human Factors Summary Evaluation Report showed that the product is reasonably safe and effective for the intended users, uses and environments.

2.5.1. Discussion on clinical safety

The two phase 3 studies performed with more than 200 patients per treatment group each provide a robust safety data base for the biosimilar insulin glargine MK-1293. The incidence and nature of adverse events was highly similar between MK-1293 and the comparator Lantus (sourced from EU as requested by the CHMP biosimilar guideline). Serious events were rare; two deaths occurred in one study which were unrelated to study drug. As expected for an insulin, the most prominent adverse events were hypoglycaemia. The latter was investigated in more detail according to the established subcategories of severity. No relevant differences between MK-1293 and Lantus became obvious.

The main focus of safety assessment of a biosimilar product lies on immunogenicity. The applicant has determined the percentage of patients who developed antibodies against insulin glargine during the study and has followed the development of antibody titres. Furthermore, it was determined in vitro whether the antibodies formed were neutralising. The screening and confirmatory anti-drug antibody assays (standard bridging electrochemiluminescence (ECL) immunoassay on the Meso Scale Discovery (MSD) platform) as well as the cell-based Nab assay to determine the neutralising potential of insulin glargine are appropriately validated and suitable for their intended use.

There was no hint that MK-1293 is more antigenic than Lantus.

2.5.2. Conclusions on clinical safety

Safety and tolerability of MK-1293 and Lantus were comparable. The number of patients who became antibody-positive during study treatment was also similar between MK-1293 and Lantus. Therefore, safety data with MK-1293 was considered satisfactory by CHMP.

2.6. Pharmacovigilance

Risk Management Plan

Safety concerns

Important identified risks	• Hypoglycaemia • Medication errors (incorrect insulin) • Injection site reactions • Hypersensitivity reactions
Important potential risks	• Malignancies • Immunogenicity

Important identified risks	• Hypoglycaemia • Medication errors (incorrect insulin) • Injection site reactions • Hypersensitivity reactions
	• Underdosing due to needle blockage
Missing information	None

Pharmacovigilance plan

No additional pharmacovigilance activities proposed. Routine pharmacovigilance is sufficient to identify and characterise the safety concerns of the product.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Hypoglycaemia	SmPC, Package leaflet, Instructions for Use	None
Medication errors (incorrect insulin)	SmPC, Package leaflet, Instruction for Use	None
Injection site reactions	SmPC, Package leaflet, Instructions for Use	None
Hypersensitivity reactions	SmPC, Package leaflet	None
Important Potential Risks		
Malignancies	None proposed. Medication available by prescription only.	None
Immunogenicity	SmPC, Package leaflet	None
Underdosing due to needle blockage	SmPC, Package leaflet, Instructions for Use	None

Conclusion

The CHMP and PRAC considered that the risk management plan version **1.2** is acceptable.

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.

PSUR submission

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.

2.7. Product information

2.7.1. User consultation

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

The PL is in line with the PL of the reference. The Applicant has successfully conducted a focus user testing on the Insuline glargine MSD PIL and pen IFU pertaining to the sections which are unique to MK-1293 drug product formulation in the glass cartridge and the pen-injector device. Specific questions were raised in relation to the risk of insulin mix-ups.

2.7.2. Quick Response (QR) code

A request to include a QR code in the labelling for the purpose of including statutory information (the instructions for use from the package leaflet) compliant with the approved version has been submitted by the applicant and has been found acceptable.

3. Benefit-risk balance

3.1. Therapeutic Context

For a biosimilar medicinal product, it is required to show similarity with the reference product, which allows extrapolation, with regard to patient benefit per se, to the efficacy and safety experience gained with the reference medicinal product. According to the relevant EMA guideline (EMEA/CHMP/BMWP/32775/2005_Rev. 1), biosimilarity for an insulin with its reference product is established via a head-to-head comparison of physicochemical and functional characteristics, time-concentration and time-action profiles in at least one glucose clamp study and, tentatively, a safety/immunogenicity study.

The biosimilar comparability programme for Lusduna (referred to MK-1293 throughout this report) consists of an extensive quality, non-clinical and clinical data package including in vitro and in vivo non-clinical studies, two single s.c. dose glucose clamp studies, one in healthy subjects (P002) and one in patients with T1DM (P005), and two phase 3 studies, one in patients with T1DM (P003) and one in patients with T2DM (P006). Predefined primary PK and PD endpoints in the clamp studies exceeded the requirements of the respective guideline. The clamp studies are considered pivotal for the demonstration of similar efficacy. According to the guideline, the specific focus of the safety study should be on the comparison of immunogenicity. However, for the purpose of powering the study, HbA1c can be used as primary endpoint as done in the studies P003 and P006.

3.2. Favourable effects

The analytical comparison shows a high degree of similarity between MK-1293 and Lantus except for minor differences in the impurity profile, which have been justified. Overall the level of impurities is equivalent or even lower in the proposed biosimilar compared to Lantus.

Based on the analytical data, similarity between MK-1293 and the EU reference product Lantus is considered demonstrated on the quality level.

Non-clinical tests demonstrated the comparability of MK-1293 and Lantus at the levels of insulin receptor (IR) binding, IR activation and metabolic activity in vitro (three different assays), following the CHMP biosimilar insulin guideline.

PK/PD studies are pivotal for the demonstration of similar efficacy of the two insulins because they are more sensitive to detect product-related differences than efficacy studies using HbA1c as endpoint.

The two comparative glucose clamp studies demonstrated PD and PK similarity between representative commercial MK-1293 cartridge formulation DP and the reference product Lantus, both in healthy subjects (P002) and in subjects with T1DM (P005).

The two phase 3 clinical studies showed equivalence with regard to Hb1c change from baseline at week 24 between MK-1293 and Lantus in both T1DM (P003) and T2DM (P006) subjects and this was achieved at similar week 24 insulin doses. The results on the secondary endpoints (fasting plasma glucose, HbA1c goals) generally support the primary outcome. These data are consistent with the phase I results demonstrating PD and PK similarity between MK-1293 and Lantus. These data support the conclusion that the efficacy profile of MK1293 is similar to that of Lantus. Results of phase B of study P003, which were submitted with the D120 Response Document, also supported the conclusion of similar efficacy of MK-1293 compared to Lantus in the longer-term.

3.3. Uncertainties and limitations about favourable effects

None

3.4. Unfavourable effects

For a biosimilar insulin the main focus of clinical safety assessment lies on immunogenicity. Furthermore, the adverse event (AE) profile should be compared in the two Phase 3 trials performed, including events of special interest for insulin, namely hypoglycaemia. No relevant differences in the profile and frequencies of AEs, including serious AEs, could be detected. The same is true for hypoglycaemia (total events as well as subcategories of severity).

In order to address immunogenicity, the Applicant measured formation and titres of anti-insulin antibodies (AIA),tested their neutralising potential, collected potential hypersensitivity reactions and looked for potential clinical signs of neutralising antibodies (i.e. markedly increased insulin demand or worsening glycaemic control which cannot be explained otherwise).

The percentage of patients who had antibodies at baseline and who developed antibodies during study treatment with MK-1293 or Lantus was comparable between the treatment groups, in the T1DM as well as in the T2DM study. Neutralising antibodies were measured by the in-vitro test used in a small number of patients with no relevant differences between the treatment groups. The antibody titres were comparable between the MK-1293 and Lantus group at all time-points tested in the T1DM study. There were no hints for formation of clinically relevant neutralising anti-insulin antibodies.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Demonstration of physicochemical similarity is required for any biosimilar development and has been established for MK-1293. Differences are observed in the impurity profile, which can be expected with different manufacturing processes but these differences are minor and do not preclude the conclusion of analytical similarity.

Demonstration of PK/PD similarity by euglycaemic clamp studies (studies P002 and P005) is considered key for the assessment of similar efficacy. Demonstration of achievement of similar glycaemic control with similar insulin doses within the phase 3 studies supports the favourable outcome of the clamp studies performed.

Based on structural, functional and PK/PD similarity of MK-1293 and Lantus, adverse events that result from exaggerated pharmacological actions can be expected to occur at similar frequencies. This assumption is confirmed by the results of the two phase 3 studies.

In addition, no relevant differences in the frequency or titres of anti-drug antibodies were found.

3.6.2. Balance of benefits and risks

Lusduna has a structural, functional, pharmacological and safety/immunogenicity profile comparable to that of the reference product Lantus.

3.6.3. Additional considerations on the benefit-risk balance

None

3.7. Conclusions

The overall B/R of Lusduna is positive.

4. Recommendation

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

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

Not applicable.

These conditions fully reflect the advice received from the PRAC.