CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 210605
Supporting document/s:	SDN1, SN000
Applicant's letter date:	April 27, 2016
CDER stamp date:	May 31, 2016
Product:	MYL-1501D (Insulin glargine) SEMGLEE (proposed name)
Indication:	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
Applicant:	Mylan GmbH
Review Division:	Division of Metabolism and Endocrinology Products
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TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

Mylan GmbH (hereafter referred to as the 'Applicant') is seeking approval of Insulin Glargine Injection (hereafter referred to by the code-name 'MYL-1501D'), a recombinant human basal insulin, for the treatment of patients with diabetes mellitus. The Applicant seeks to rely, in part, on prior approval of the U.S. listed drug Lantus (insulin glargine for injection – NDA 021081, which will be referred to hereafter as 'Lantus-US') via the 505(b)(2) regulatory pathway.

MYL-1501D shares the amino acid sequence with Lantus-US, but unlike Lantus-US that is produced in *E. coli*, MYL-1501D is produced in *Pichia pastoris*. The to-be-marketed formulation of MYL-1501D contains insulin glargine drug substance manufactured in Malaysia (referred to hereafter as 'Process VI'), whereas most of the nonclinical studies (and clinical studies) except the in vitro and in vivo pharmacology studies and a repeat dose 28-day rat toxicity study were performed with of MYL-1501D containing insulin manufactured in India (referred to hereafter as 'Process V').

The excipients in MYL-1501D Processes V and VI are the same as those used in the listed drug (Lantus-US), and the amounts are similar (refer to section 2.3.1). There are no substantive differences in excipients from a safety perspective.

MYL-1501D is administered either via a disposable, variable-dose, multiple-dose pen injector intended for self-administration via subcutaneous injection or from a vial via a standard insulin syringe. MYL-1501D for the pen presentation is formulated in a glass cartridge, while a pen injector device delivers the formulation.

The Applicant compared MYL-1501D (Process VI) to the listed drug, Lantus-US by performing head-to-head in vitro and in vivo pharmacology studies and repeat dose toxicity studies. The chosen container and container closure systems (glass cartridge, rubber plunger and (b) (4) rubber seal) and the vials (glass vial, rubber stopper) were evaluated for their compatibility with the final MYL-1501D drug product.

1.1 Recommendations

1.1.1 Approvability

From a Pharmacology/Toxicology perspective, this 505(b)(2) new drug application for MYL-1501D is approvable.

1.1.2 Additional Nonclinical Recommendations

No additional recommendations.

1.1.3 Labeling

The labeling for MYL-1501D should be identical to the approved Lantus-US product labeling, except for the proprietary name, see Appendix.

1.2 Brief Discussion of Nonclinical Findings

Multiple MYL-1501D nonclinical/clinical formulations were tested during the product development phase. An earlier MYL-1501D drug substance manufactured in India (Process V) was replaced by to-be-marketed MYL-1501D drug substance manufactured in Malaysia (Process VI) late in product development. While the Applicant conducted many nonclinical studies with Process V MYL-1501D drug substance, the Applicant conducted head-to-head nonclinical in vitro and in vivo studies with both Process VI insulin and Lantus-US that were sufficient in scope to support the NDA submission.

The nonclinical development program of MYL-1501D was designed to establish similarity of MYL-1501D to Lantus-US, such that reliance on the Agency's previous findings of safety and efficacy for Lantus-US was justifiable. More specifically, the Applicant utilized a battery of in vitro pharmacology assays, in vivo pharmacodynamic (PD) and pharmacokinetic (PK) studies, along with in vitro insulin receptor (IR), insulin-like growth factor-1 receptor (IGF-IR) binding studies, cell-based receptor-dependent metabolism and mitogenicity studies, and a repeat-dose rat toxicity study to compare MYL-1501D and Lantus-US.

Pharmacodynamic and safety profile of MYL-1501D

In vitro pharmacology studies assessed multiple batches of the to-be-marketed MYL-1501D formulated with Process VI drug substance via direct comparison to Lantus-US in binding and functional assays designed to establish comparability. These studies included 1) kinetic binding assays of MYL-1501D and Lantus-US to insulin receptors A and B form (IR-A and IRB), 2) IR-A and IR-B phosphorylation assays, and 3) assessments of glucose uptake from the medium by differentiated mouse 3T3-L1 adipocyte cells to evaluate metabolic potency. Secondary PD studies included 1) binding to purified IGF-1R, and 2) evaluation of mitogenic potential. These studies generally established comparability across multiple batches of MYL-1501D (Process VI) and Lantus-US. In order to compare MYL-1501D manufactured from Process V to that from Process VI versus Lantus-US, the Applicant submitted a 28-day toxicity study by subcutaneous route in Wistar rats.

The binding, phosphorylation, potency, secondary pharmacology studies comparing ML-1501D and Lantus-US indicated that the two were comparable. Furthermore, the NOAELs and toxicologic profiles for MYL-1501D and Lantus-US were concluded to be sufficiently similar. Therefore, it was concluded that the two products are comparable from a nonclinical perspective.

Immunogenicity

Nonclinical immunogenicity assessments were not conducted. However, MYL-1501D and Lantus-US produced similar pharmacodynamic glucose lowering in the 28-day comparative toxicity study in rats and therefore there was no evidence of formation of neutralizing antidrug antibodies. The types of immune responses regarded as a concern for humans (e.g., innate immunity) cannot be predicted based on animal data.

Excipients of toxicological concern

No studies were required to qualify excipients, as no significant differences exist between those in MYL-1501D and Lantus-US.

Container closure system compatibility

Based on the results obtained from the extractable, screening leachable and formal leachable studies, the chosen container closure system (glass cartridge, rubber plunger and (b) (4) rubber seal) is compatible with the MYL-1501D drug product. Overall, the container closure system consists of components that are standard for parenteral use. CDRH reviewed the Pre-Filled Pen at the request of CDER, and noted the biocompatibility information provided by the applicant to evaluate cytotoxicity, sensitization, and irritation endpoints of the user contact was appropriate and acceptable for the intended use of the user contacting of the combination product.

Pregnancy

No studies were required based on the established similarity of MYL-1501D to the listed drug Lantus-US. The following is from the approved Lantus-US labeling. Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m2. In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m2, were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal. *In a*

Carcinogenesis and Mutagenesis, Impairment of Fertility

No studies were required based on the established similarity of MYL-1501D to the listed drug Lantus-US. In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which was for the rat approximately 10 times and for the mouse approximately 5 times the recommended

human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m2. The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which was approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m2, maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH insulin.

2 Drug Information

2.1 Drug

MYL-1501D (SEMGLEE)

2.1.1 CAS Registry Number (Optional)
160337-95-1

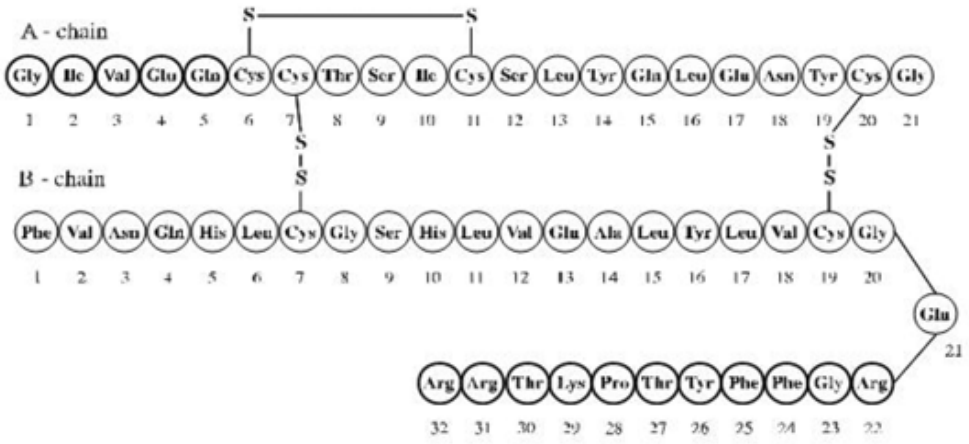
2.1.2 Generic Name
Insulin glargine

2.1.3 Code Name
MYL-1501D

2.1.4 Chemical Name
21A-Glycine-30Ba-L-arginine-30Bb-L-arginine-insulin (human)

2.1.5 Molecular Formula/Molecular Weight
$C_{267}H_{404}N_{72}O_{78}S_6$

2.1.6 Structure



2.1.7 Pharmacologic class

Long-acting human insulin analog

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA 021081, Sanofi, Lantus-US (insulin glargine injection)

2.3 Clinical Formulation

2.3.1 Drug Formulation

MYL-1501D (insulin glargine) is manufactured using *Pichia pastori* and has the same mass, amino acid sequence and di-sulfide bond pairing as that of insulin glargine in Lantus-US (manufactured in *E. coli*). Insulin glargine provides approximately 24 hours of basal insulin coverage with a generally flat time x action profile over this period. (b) (4)

(b) (4)

(b) (4). Zinc is included in the formulation (b) (4)

(b) (4) of insulin glargine.

Table 1: Composition of MYL-1501D Drug Product

Component	Quantity/mL	Quantity per 3 mL cartridge	Quality standard	Function
Insulin glargine	100 units	300 units	In-house	Active ingredient
m-Cresol	(b) (4)		USP and Ph. Eur.	(b) (4)
Glycerol (85% (b) (4)			Ph. Eur.	
Zinc (b) (4)			USP and Ph. Eur.	
Hydrochloric acid			USP and Ph. Eur.	pH adjustment
Sodium hydroxide			USP and Ph. Eur.	pH adjustment
Water for injection			USP and Ph. Eur.	(b) (4)
Ph. Eur= European Pharmacopoeia; q.s.= quantity sufficient; USP= United States Pharmacopeia.				
[1]Zinc quantity is calculated (b) (4) to make the final quantity of zinc 30 µg/100 units of insulin glargine.				

MYL-1501D drug product (DP) (vials) batches manufactured by Biocon Sdn. Bhd. (Johor, Malaysia) were analyzed and found to comply with USP monograph of "Insulin Glargine Injection".

Table 2: MYL-1501D Drug Product Batch Analysis based on USP Monograph of 'Insulin Glargine Injection'

Batch No. [Cartridge]		BS16002122	BS16002123	BS16002124
Manufacturing Date		June 2016	June 2016	June 2016
Batch Size		(b) (4)		
Fill Volume and Presentation		10 mL vial	10 mL vial	10 mL vial
Usage of batch		Process Validation	Process Validation	Process Validation
Corresponding Drug Substance Batch No.		BS15007170	BS15007370	BS15007370, BS15006908
DS manufacturing process		VI	VI	VI
Tests	**Acceptance criteria**	**Results**		
Description	A clear colorless solution free from any particulate matter	A clear colorless solution free from any particulate matter	A clear colorless solution free from any particulate matter	A clear colorless solution free from any particulate matter
Identification	The retention time of the major peak of the sample solution corresponds to that of the standard solution, as obtained in the assay	Complies	Complies	Complies
pH	3.5 – 4.5	(b) (4)		
Limit of high molecular weight proteins	NMT 0.5%^	(b) (4)	BQL	(b) (4)
Zinc Determination (By Atomic absorption spectroscopy)	20 – 40 µg/mL^	(b) (4)		
(b) (4)	Between (b) (4) mg/mL and (b) (4) mg/mL (Between (b) (4) (b) (4)% of the label claim)	(b) (4)		
Particulate contamination (visible particulate)	Physical inspection should not show any evidence of foreign particles or any other contamination	Complies	Complies	Complies
*Extractable volume	(b) (4)			

2)**Table 2: (cont.)**

Batch No. [Cartridge]		BS16002122	BS16002123	BS16002124
Assay (By HPLC) Content of Insulin Glargine	(b) (4) USP Insulin Glargine Units/mL (Between (b) (4) (b) (4) of the label claim)	(b) (4)		
Related Proteins				
Any individual impurity	Any individual insulin glargine related protein: NMT 0.5%	(b) (4)		
Total impurities	Total insulin glargine related proteins: NMT 2.0%			
***Seal integrity test**	None of the Cartridges should contain any trace of colored solution	Complies	Complies	Complies
Particulate matter in injection				
≥ 10 µm	Not more than (b) (4) particles/container	(b) (4)		
≥ 25 µm	Not more than (b) (4) particles/container			
Bacterial endotoxin Test	NMT 80 USP Endotoxin Units/ 100 USP Insulin Glargine Units	Less than (b) (4) EU/ 100 U of insulin glargine	Less than (b) (4) EU/ 100 U of insulin glargine	Less than (b) (4) EU/ 100 U of insulin glargine
Sterility Tests	Preparations for injection meets the requirements of sterility	Complies	Complies	Complies

*The sample complies with the above test as per in-house specification based on batch release data. All the other samples complies with the above test as per USP specifications

^ The limits are based on published "USP Interim Revision Announcement Official November 1, 2016" from the "United States Pharmacopeial Convention"

BDL= Below Detection Level; BQL= Below Quantitation Level; EU= Endotoxin Unit; ISO= International Organization for Standardization; LOD= Limit of Detection; LOQ= Limit of Quantitation; NMT= Not More Than

2.3.2 Container Closure Presentations of the Drug Product

MYL-1501D drug product is available in the following two presentations:

1) **MYL-1501D (Insulin Glargine) – Pre-Filled Pens**

The excipients in the MYL-1501D DP formulation presented in Pre-Filled Pens are identical to those used in the listed drug (Lantus-US) Pre-Filled Pens.

The Pre-filled pen (with integrated 3-mL colorless tubular glass [USP Type I] cartridges sealed using (b) (4) seals and plugged with (b) (4) plunger stoppers) is a manual use, disposable, multiple and variable dose injection device.

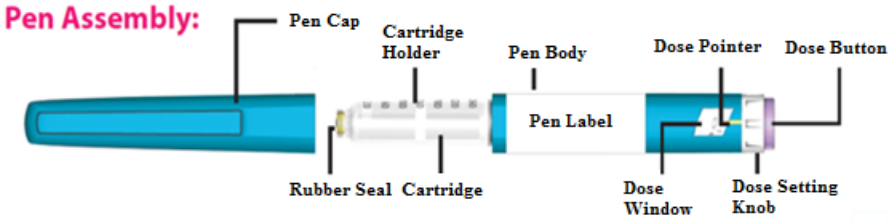


Figure 1: Representative Diagram of MYL-1501D Drug Product Presented as Pre-Filled Pen

Based on the results obtained from the extractable, screening leachable and formal leachable studies, the chosen container closure system (glass cartridge, rubber plunger and (b) (4) rubber seal) is compatible with MYL-1501D DP. Overall, the container closure system is composed of components that are standard for parenteral use.

CDRH reviewed the Pre-Filled Pen at the request of CDER, and noted in its review that "the user contact of the pen injector is categorized as surface contact with intact skin. The provided biocompatibility information to evaluate cytotoxicity, sensitization, and irritation endpoints of the user contact is appropriate and acceptable for the intended use of the user contacting of the combination product."

2) **MYL-1501D (Insulin Glargine) – 100 U/mL – Solution for injection in Vials**

The excipients in the MYL-1501D DP formulation presented in vials are identical to those used in the listed drug (Lantus-US) presented in vials.

MYL-1501D DP contains 100 units/mL of insulin glargine presented in a 10 mL clear tubular glass (Type I United States Pharmacopeia [USP]/Ph. Eur.) vial closed with a

(b) (4) rubber stopper and sealed using a flip-off seal. The flip-off seals do not come in contact with the drug product.

2.3.3 Comments on Novel Excipients

All the excipients used in the manufacture of MYL-1501D DP are USP, and are the same as those used in the listed drug, Lantus-US.

The excipients in the MYL-1501D DP formulation presented in Pre-Filled Pens are identical to those used in the listed drug (Lantus-US) presented in Pre-Filled Pens.

Table 3: Excipients Used in the Manufacture of MYL-1501D Drug Product

Sr. No.	Name of Excipient	Compliance with Quality Standard
1	*m*-Cresol*	Ph. Eur. and USP
2	Glycerol (85%)	Ph. Eur.
3	Zinc (b) (4)	Ph. Eur. and USP
4	Hydrochloric acid	Ph. Eur. and USP
5	Sodium hydroxide	Ph. Eur. and USP
6	Water for injection	Ph. Eur. and USP
(b) (4)		

The excipients in the MYL-1501D DP formulation presented in vials are identical to those used in the listed drug (Lantus-US) presented in vials.

Table 4: Excipients Used in the Manufacture of MYL-1501D Drug Product in 10 mL Vials

Component	Quantity/mL	Quantity/10 mL (vial)	Quality standard	Function
Insulin glargine	100 units[2]	1000 units[2]	In-house	Active ingredient
m-Cresol	2.7 mg	27 mg	Ph. Eur. and USP	(b) (4)
Glycerol (85% (b) (4)	20 mg	200 mg	Ph. Eur.	
Zinc[1] (b) (4)	30 µg	300 µg	Ph. Eur. and USP	
Polysorbate-20	(b) (4)		Ph. Eur. and USP	
Hydrochloric acid			Ph. Eur. and USP	pH adjustment
Sodium hydroxide			Ph. Eur. and USP	pH adjustment
Water for injection			Ph. Eur. and USP	(b) (4)

Ph. Eur: European Pharmacopoeia; q.s.: quantity sufficient; USP: United States Pharmacopeia.

[1]Zinc quantity is calculated (b) (4) to make the final quantity of zinc 30 µg/100 units of insulin glargine.

[2]100 units of insulin glargine corresponds to 3.64 mg of insulin glargine

2.3.3 Comments on Impurities/Degradants of Concern

Product-related Impurities

The probable product-related impurities that may be formed due to the inherent nature of the (b) (4) (b) (4) MYL-1501D drug substance (DS) are summarized in Tables 5 and 6. There is a low level of concern regarding the safety of insulin derived breakdown products.

Table 5: Probable Product-related Impurities and Substances Formed During Manufacture of MYL-1501D Drug Substance

Product related impurities	Identity	Theoretical mass (±1 Da)	Structure
Precursor related	(b) (4)		
Glycosylated species			
Sequence species			
Deamidation /Acetylation			

MYL-1501D (Insulin Glargine)

Manufacturer: Biocon Sdn. Bhd. (Johor, Malaysia)

3.2.S.3.2 Impurities

Product related impurities	Identity	Theoretical mass (±1 Da)	Structure
	(b) (4)		

The amount of product-related impurities present in the final DS is presented in Table 6 for representative batches from Process VI.

Table 6: Related Compounds (Method A) Impurities in Drug Substance

RRT Range	Probable Mass identity	Process VI (%)		
		BS15005128	BS15005256	BS15005423
(b) (4)				

RRT Range	Probable Mass identity	Process VI (%)		
		BS15005128	BS15005256	BS15005423
(b) (4)				
(b) (4)				

The microbial content of MYL-1501D (Process VI) Manufacturer: Biocon Sdn. Bhd. (Johor, Malaysia) is provided below.

Table 7: Microbial content of MYL-1501D (Process VI) of representative batches at release

Test Parameter		BS15006908	BS15007049	BS15007170
Microbial load (cfu/mL)	Total bacterial count	Less than (b) (4) cfu/g	Less than (b) (4) cfu/g	Less than (b) (4) cfu/g
	Total yeast & molds count	Less than cfu/g	Less than cfu/g	Less than cfu/g
BET (EU/mL)		Less than (b) (4) EU/mg	Less than (b) (4) EU/mg	Less than (b) (4) EU/mg

No impurities in the drug substance were deemed a significant clinical safety concern.

Probable Product-related Impurities and Substances Formed During Manufacture of MYL-1501D Drug Product

The (b) (4) glass cartridge used in a primary closure system for insulin was examined for chemical compounds, which can be released under exaggerated extraction conditions. The extracts were analyzed by Inductive Coupled Plasma/Optical Emission Spectroscopy (ICP/OES) for element analysis. The results showed (b) (4) (b) (4) (b) (4). None of these elements are included in the, "Recommendations for Elements to be Considered in the Risk assessment" in the Guidance, ICH Q3D ELEMENTAL IMPURITIES GUIDANCE FOR INDUSTRY (September, 2015).

Table 8: Recommendations for Elements to be Considered in the Risk Assessment (per ICH Q3D*)

Table V.1 (5.1): Elements To Be Considered in the Risk Assessment

Element	Class	If intentionally added (all routes)	If not intentionally added		
			Oral	Parenteral	Inhalation
Cd	1	yes	yes	yes	yes
Pb	1	yes	yes	yes	yes
As	1	yes	yes	yes	yes
Hg	1	yes	yes	yes	yes
Co	2A	yes	yes	yes	yes
V	2A	yes	yes	yes	yes
Ni	2A	yes	yes	yes	yes
Tl	2B	yes	no	no	no
Au	2B	yes	no	no	no
Pd	2B	yes	no	no	no
Ir	2B	yes	no	no	no
Os	2B	yes	no	no	no
Rh	2B	yes	no	no	no
Ru	2B	yes	no	no	no
Se	2B	yes	no	no	no
Ag	2B	yes	no	no	no
Pt	2B	yes	no	no	no
Li	3	yes	no	yes	yes
Sb	3	yes	no	yes	yes
Ba	3	yes	no	no	yes
Mo	3	yes	no	no	yes
Cu	3	yes	no	yes	yes
Sn	3	yes	no	no	yes
Cr	3	yes	no	no	yes

*The above Table reproduced from Q3D ELEMENTAL IMPURITIES GUIDANCE FOR INDUSTRY (2015).

The elemental impurities in the DP are very low and do not represent a safety concern at the proposed clinical dose.

Based on the results obtained from the extractable, screening leachable and formal leachable studies, the chosen container closure system (glass cartridge, rubber plunger and (b) (4) rubber seal) is compatible with MYL-1501D DP. Overall, the container closure system is composed of components that are standard for parenteral use.

An analyses of leachables found in MYL-1501D after storage for 1 month at 40°C in direct contact with a glass vial sealed with a (b) (4) rubber closure was performed to compare the contact solution with a blank solution using (b) (4)

screening, *GCIMS* screening and UPLCIMS screening. No differential volatile, semi-volatile or non-volatile organic compound were detected above the reporting limit of [(b) (4)] or [(b) (4)] µg/L *(GC/MS* and UPLCIMS). Element analysis by ICP/OES demonstrated an increased concentration of [(b) (4)] in the contact solution compared to the blank solution. No [(b) (4)] was detected in the contact solution or blank solution. These impurities level are very low and do not represent a safety concern.

Table 9: Specifications for MYL-1501D Drug Product (3 mL Cartridges)

Sr. No.	Parameter	Test Method Reference	Acceptance Criteria
1	Description	Visual inspection/In-house	A clear colorless liquid free from turbidity and foreign matter
2	Identification (by HPLC)	In-house (based on Ph. Eur. method # 2.2.29 and # 0838 and USP <621>)	The retention time of the principal peak of the sample obtained in assay chromatogram should be comparable with that of the standard
3	pH of the solution	In-house (based on Ph. Eur. method # 2.2.3 and USP <791>	Between [(b) (4)]

Sr. No.	Parameter	Test Method Reference	Acceptance Criteria
4	High molecular weight impurities (by size exclusion chromatography)	In-house (based on Ph. Eur. method # 2.2.30 and USP <621>)	Not more than [(b) (4)]
5	Zinc content (by atomic absorption spectrometry)	In-house (based on Ph. Eur. method # 2.2.23 and USP <852>)	[(b) (4)] µg/100 Units
6	[(b) (4)]	In-house (based on USP <621>)	Between [(b) (4)] (between [(b) (4)] % of the label claim*)
7	Particulate matter (visible particulate)	Based on Ph. Eur. method #2.9.20 and USP <790>	Physical inspection should not show any evidence of foreign particles
8	Extractable volume	Based on Ph. Eur. method # 2.9.17 and USP <1>	Between [(b) (4)]
9	Assay (by HPLC) (content of insulin glargine)	In-house (based on USP <621>)	Between [(b) (4)] (between [(b) (4)] % of the label claim**)
10	Related Compound (by HPLC)		
	Total impurities	In-house (based on USP <621>)	Not more than [(b) (4)] %
	Any individual impurity		Not more than [(b) (4)] %

The Applicant provided analytical evaluation threshold (AET) from the leachable studies performed with container closure system. The AET values from the screening leachable study is summarized from the CMC review.

In a screening, leachable study of the container closure system, the impurities are estimated to be [(b) (4)] µg/mL at the maximum daily dose of 1 mL/day. This is less than the [(b) (4)] µg/day specified for genotoxic impurities and are considered safe at the

proposed clinical doses. Based on the results from the extractable and screening leachable studies, it is concluded that the chosen container closure systems (glass cartridge, rubber plunger and (b) (4) rubber seal) and the vials (glass vial, rubber stopper) are compatible with MYL-1501D.

2.4 Proposed Clinical Population and Dosing Regimen

MYL-1501D is proposed to be indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM). Drug will be administered subcutaneously once daily at any time of day, but at the same time every day. Dosage is Individualized based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use.

2.5 Regulatory Background

Biocon SA opened IND 105279 on December 14, 2011. On May 31, 2016 Mylan GmbH submitted NDA 210605 for MYL-1501D. The applicant's insulin glargine drug is already marketed in India under the trade name, Basalog®. Regulatory Background relating to the nonclinical issues during the drug development is summarized in the following section.

FDA communicated to the Applicant under IND 105279 and NDA in response to the sponsor/Applicant questions. FDA provided nonclinical data requirements to establish comparability of the Applicant's drug formulation to the Lantus US on October 22, 2012, April, 7, 2014, and November 11, 2016. In view of Applicants intent to use 505(b)(2) pathway for MYL-1501D, FDA provided information on the requirements to establish comparability to the proposed listed drug, Lantus-US. This included the requirement to establish comparability by in vitro binding and metabolism, studies, in vitro and in vivo pharmacokinetic, pharmacodynamic studies, to establishment the safety of impurities and leachables, and for repeat dose toxicity studies to establishment comparability of with Lantus-US. It was emphasized that the Applicant needs to conduct these studies comparing the clinical formulation of MYL-1501D with the U.S.-approved comparator drug, Lantus-US.

3 Studies Submitted

During the development of MYL-1501D, the Applicant used four different MYL-1501D formulations. Tables 10 and 11 show the composition of each formulation as well as the composition of Lantus-US (or Lantus approved in the European Union, referred to hereafter as 'Lantus-EU') used as the comparator product. All formulations contained the same concentration of insulin glargine, 100 U/mL. The inactive ingredients in the formulations (*m*-cresol, (b) (4) polysorbate-20, glycerol, zinc (b) (4), sodium hydroxide, and hydrochloric acid) comply with applicable USP standards and are commonly used in parenteral formulations.

Table 10: Composition of MYL-1501D Formulations and Lantus-US Used During Development

Excipient[a] (amount/mL)	MYL-1501D Formulation				Comparator	
	A	B	C	D[b]	Lantus-IN[c]	Lantus-US, Lantus-EU, and Lantus-JP[d]
Insulin glargine	100 Units	100 Units	100 Units	100 Units	100 Units	100 Units
m-Cresol	2.7 mg	--	2.7 mg	2.7 mg	2.7 mg	2.7 mg
						(b) (4)
Polysorbate-20	20 µg	--	--	20 µg[e]	20 µg	--
Zinc	30 µg	(b) (4)	30 µg	30 µg	30 µg	30 µg
Glycerol			(b) (4)	20 mg of 85%	(b) (4)	20 mg of 85%

a: All formulations are at pH 4.0 and also contain sodium hydroxide, hydrochloric acid, and water for injection.
(b) (4)
c: Vial formulation.
d: Cartridge/disposable pen formulations marketed in the US, EU, and Japan, respectively.
e: Polysorbate-20 content for 10 mL vial presentation.
Note: Formulation A is similar to the Lantus-IN (vial) formulation; Formulations C and D are (b) (4) similar to the Lantus-US, Lantus-EU, and Lantus-JP disposable pen/cartridge formulations.

Table 11: Studies were performed using MYL-1501D Formulations and Lantus-US Used Across Development Studies

Studies	Category	MYL-1501D Formulation[a]	Comparator (where used)[b]	Purpose of Study
Non-clinical				
In vitro IR and IGF-1R binding, IR phosphorylation, metabolic potency, and mitogenic potency assays	Pivotal	D	Lantus-US and Lantus-EU	To compare in vitro primary and secondary PD of MYL-1501D and Lantus (-US and -EU) across multiple batches
In vivo quantitative rabbit blood sugar assays	Pivotal	D	Lantus-US and Lantus-EU	To compare relative potency of MYL-1501D and Lantus (-US and -EU) across multiple batches
Study G11066: 28-Day repeat-dose toxicity in rats	Pivotal	C	Lantus-US and Lantus-EU	To compare 28-day repeat-dose toxicity, PD, toxicokinetics, local tolerance, immunogenicity, and NOAEL between MYL-1501D, Lantus-US, and Lantus-EU
Study U-16176: 28-Day repeat-dose toxicity in rats	Pivotal	D	Lantus-US	To compare 28-day repeat-dose toxicity, PD, toxicokinetics, local tolerance, and NOAEL between MYL-1501D Process V, MYL-1501D Process VI, and Lantus-US
In vivo PD studies in mice and rabbits	Supportive	A and B	Lantus-IN	To compare in vivo potency/PD effect of MYL-1501D formulations and Lantus
Acute-dose toxicity in mice, rats, and rabbits	Supportive	A	Lantus-IN	To study/compare acute toxicity
90-Day repeat-dose toxicity in rats and rabbits	Supportive	A	Lantus-IN	To study/compare 90-day repeat-dose toxicity, PD, toxicokinetics, local tolerance, immunogenicity, and NOAEL
Skin tolerance and allergenicity in guinea pigs	Supportive	A	N/A	To study local tolerance and allergenicity

Studies	Category	MYL-1501D Formulation[a]	Comparator (where used)[b]	Purpose of Study
				Lantus-EU.
MYL-1501D-1001: PK/PD clamp study in T1DM (Germany)	Pivotal	D	Lantus-US	To compare PK and PD parameters and safety between MYL-1501D Process V, MYL-1501D Process VI, and Lantus-US.
MYL-GAI-3001: safety, efficacy, and immunogenicity study in T1DM (Global)	Pivotal	D	Lantus-US	To compare efficacy, immunogenicity, and safety of MYL-1501D with that of Lantus-US
MYL-GAI-3002: safety, efficacy, and immunogenicity study in T2DM (Global)	Pivotal	D	Lantus-US	To compare efficacy, immunogenicity, and safety of MYL-1501D with that of Lantus-US
MYL-GAI-3003: safety and efficacy study in T1DM (Global)	Supportive	D	Lantus-US	To evaluate interchangeability of MYL-1501D with that of Lantus-US
FFP-112-01: PK/PD clamp study in NHV (Japan)	Supportive	D	Lantus-JP	To compare the PK/PD characteristics and safety of MYL-1501D and Lantus-JP
FFP-112-02: safety, efficacy, and immunogenicity in T1DM (Japan)	Supportive	D	Lantus-JP	To compare efficacy, immunogenicity, and safety of MYL-1501D with that of Lantus-JP
CLG031/BIO012/DM/GLA/2007: Safety, efficacy, and immunogenicity in T1DM (India)	Supportive	B	Lantus-IN	To compare the safety and efficacy of MYL-1501D with Lantus-IN

Abbreviations: IGF-1R, insulin-like growth factor-1 receptor; IR, insulin receptor; NHV, normal healthy volunteers; NOAEL, no observed adverse effect level; PD, pharmacodynamic(s); PK, pharmacokinetic(s); T1DM, type 1 diabetes mellitus.

[a]: MYL1501D (Formulation D) intended for commercialization in the EU

[b]: Lantus was sourced from the US (Lantus-US), EU (Lantus-EU), Japan (Lantus-JP), or India (Lantus-IN, Japan (Lantus-JP), or India (Lantus-IN).

The insulin drug substance in the to-be-marketed clinical formulation is produced in Malaysia by Process VI and is designated (as necessary) throughout this review as MYL-1501D (Process VI).

3.1 Studies Reviewed

All in vitro and in vivo pharmacology and in vivo toxicology studies comparing MYL-1501D (Process VI) and the listed drug, Lantus-US were reviewed. These studies were conducted to establish comparability between MYL-1501D and Lantus-US.

3.2 Studies Not Reviewed

Supportive nonclinical studies performed using formulations that are different from the proposed MYL-1501D clinical formulation (e.g., Process V) or performed with comparators that are not Lantus-US (e.g. MYL-1501D, Lantus-EU) were generally not reviewed.

Previous Reviews Referenced

None.

4 Pharmacology

4.1 Primary Pharmacology

4.1.1 In Vitro Binding to Insulin Receptors

The human insulin receptor (IR) is expressed as two isoforms IR-A (short form) and IR-B (long form). IR-B is expressed in normal adult tissues and the IR-A is expressed primarily in fetal tissues and cancerous cells. MYL-1501D was evaluated by the Applicant for its binding affinity to IR-A and IR-B in comparison to the listed drug, Lantus-US.

Insulin Receptor Long Form (IR-B) Kinetic Binding Assay

Study U-15309: Sample Analysis for Assessing the Binding Kinetics of Insulin Glargine to Insulin Receptor (Long form) Using Biacore

The study was conducted to compare the binding kinetics of different batches of MYL-1501D (processes V and VI), Lantus-US, and Lantus-EU insulin glargine to IR-B using surface plasmon resonance technology on the Biacore instrument platform in the kinetics mode. The evaluation method involved immobilizing insulin receptor ligand on a CM5 chip and passing various concentrations of insulin glargine analyte for assessing the binding kinetics. The resultant sensorgrams were analyzed for binding kinetics to establish binding between the ligand and analyte. Mean values of triplicate measures for rate of association (K_a), rate of dissociation (K_d), and dissociation constant (K_D) were similar for different batches of the MYL-1501D and Lantus-US.

Table 12: Binding Kinetics of Insulin Glargine to Insulin Receptor (Long form) Using Biacore

Drug	Ka(1Ms-1)a	Kd(1/s)a	KD(nM)a
MYL1501D (Processes V and VI)	6.41E+05 to 7.54E+05 Ms^{-1}	0.0106 to 0.0138 s-1	15.8 to 18.4 nM
Lantus-US	6.68E+05 to 7.55E+05 Ms^{-1}	0.0110 to 0.0151 s^{-1}	15.4 to 20.4 nM

Abbreviations: Ka, Rate of association; kd, Rate of dissociation; KD, Equilibrium dissociation constant; US, United States
a: Average of N=3 reported

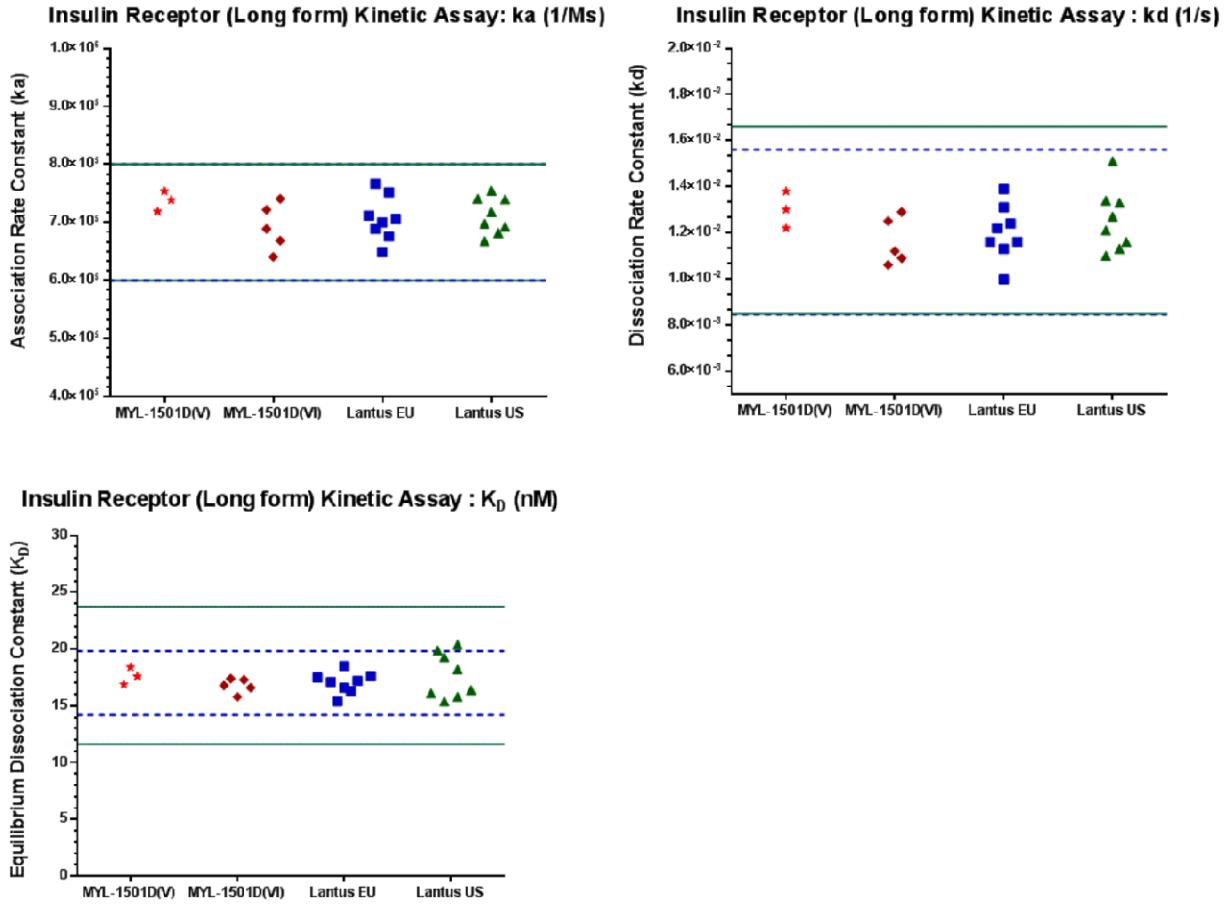


Figure 2: Insulin Receptor (Long Form) Kinetic Assay

Study U-16336: Sample Analysis for Assessing the Binding Kinetics of Insulin Glargine to Insulin Receptor (Long form) Using Biacore

The study compared the binding kinetics of different insulin glargines to IR-B using surface plasmon resonance technology on the Biacore instrument platform in the kinetics mode. The evaluation method involved immobilizing insulin receptor ligand on a CM5 chip and passing various concentrations of insulin glargine analyte for assessing the binding kinetics. The resultant sensorgrams were analyzed for binding kinetics to establish binding between the ligand and analyte. The average relative potency was highly similar across multiple batches of MYL-1501D (Process VI) and Lantus-US, as shown below.

Table 13: Kinetic Binding of MYL-1501D and Lantus (US) to Insulin Receptor Long Form (IR-B)

Test Article	k_a (1/Ms)	k_d (1/s)	K_D (nM)
MYL-1501D (range)	5.999E+05 - 6.524E+05	0.014 - 0.016	2.266E-08 - 2.362E-08
Lantus-US (range)	5.821E+05 - 7.388E+05	0.013 - 0.016	2.162E-08 - 2.824E-08

Abbreviations: k_a, association rate constant; k_d, dissociation rate constant; K_D, equilibrium dissociation constant.
Note: Eight batches of each test article were analyzed.

Insulin Receptor Short Form (IR-A) Kinetic Binding Assay

IR-A is expressed predominantly in fetal tissues and cancer cells. There is considerable evidence that IR-A binds not only insulin but also insulin-like growth factor-2, and may play a critical role in the development of breast cancer, thyroid cancer, and leiomyosarcoma. The role of the IR-A has been discussed for hybrid receptors, as increased expression of IR-A/IGF-1R hybrids has been found in tumors (Sommerfeld et al 2010)[1].

Study U-15325: Sample Analysis for assessing the binding kinetics of Insulin Glargine to Insulin Receptor (Short form) using Biacore

This study compared the binding kinetics of MYL-1501D, Lantus-US, and Lantus-EU to the IR-A using surface plasmon resonance technology on the Biacore instrument platform in the kinetics mode. The evaluation method involved immobilizing Insulin receptor ligand on a CM5 chip and passing various concentrations of Insulin Glargine analyte for assessing the binding kinetics. The resultant sensorgrams were analyzed for binding kinetics to establish binding between the ligand and analyte.

The mean values of triplicate measurements for K_a, K_d, and K_D were similar for different batches of MYL-1501D (Process V and Process VI), and Lantus-US.

Table 14: Binding kinetics of MYL1501D and Lantus-US to IR-A (Short Form)

Drug Substance	K_a(1Ms^{-1})[a]	K_d(1/s)[a]	K_D(nM)[a]
MYL1501D (Processes V and VI)	1.33 to 1.88E+06 Ms^{-1}	0.0262 to 0.0406 s^{-1}	18.8 to 23.3 nM
Lantus-US	1.18 to 1.70E+06 Ms^{-1}	0.0227 to 0.0363 s^{-1}	17.6 to 22.8 nM

Abbreviations: Ka, Rate of association; kd, Rate of dissociation; KD, Equilibrium dissociation constant; US, United States
a: Average of N=3 reported

[1] Sommerfeld MR, Muller G, Tschank G, Seipke G, Habermann P, et al. (2010) In Vitro Metabolic and Mitogenic Signaling of Insulin Glargine and Its Metabolites. PLoS ONE 5(3): e9540. oi:10.1371/journal.pone.00095400605

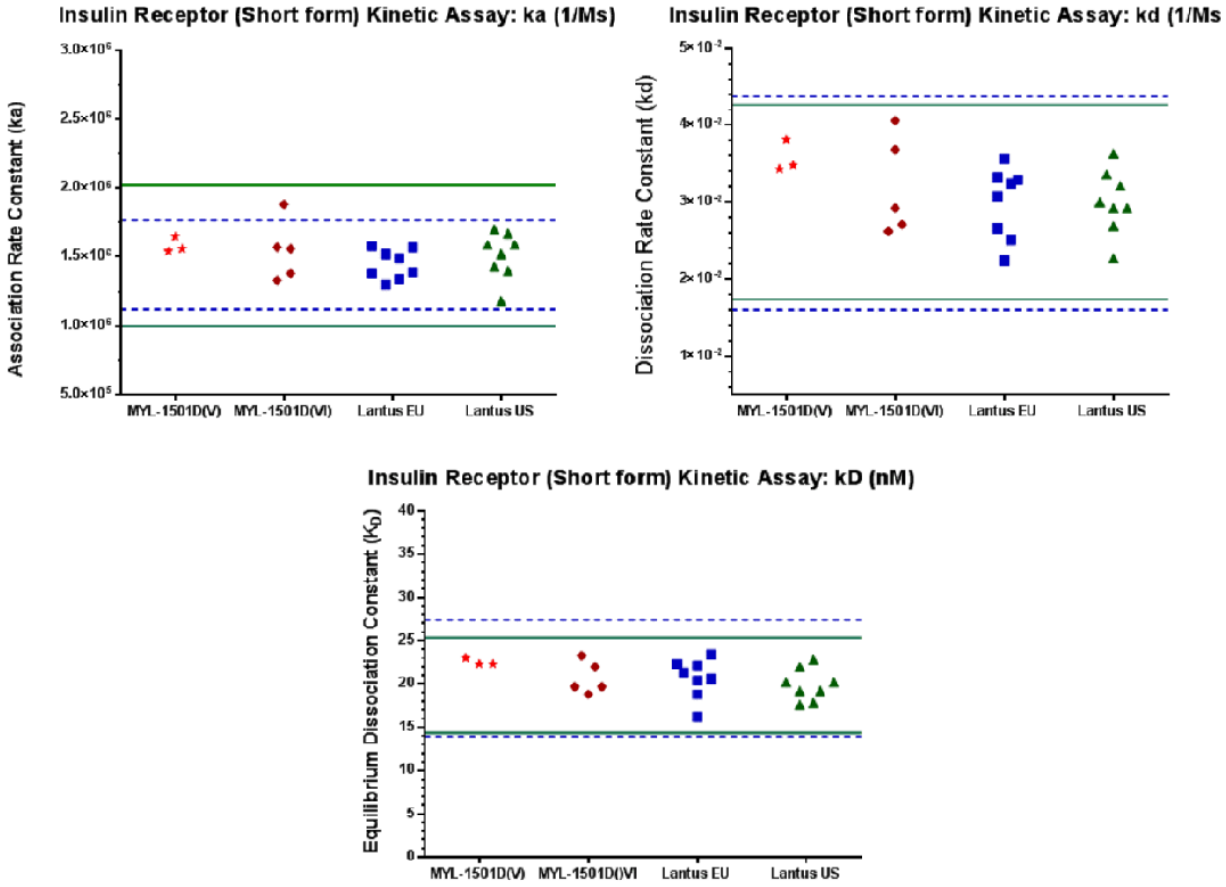


Figure 3: Insulin Receptor (Long Form) Kinetic Assay

Study U-16335: Sample Analysis for Assessing the Binding Kinetics of Insulin Glargine to Insulin Receptor (Short form) using Biacore

The study assessed the binding kinetics of MYL-1591D (Process VI) insulin glargine to IR-A using surface plasmon resonance technology on the Biacore instrument platform in the kinetics mode. The evaluation method involved immobilizing Insulin receptor ligand on a CMS chip and passing various concentrations of insulin glargine analytes for assessing the binding kinetics. The resultant sensorgrams were analyzed for binding kinetics to establish binding between the ligand and analyte.

Table 15: Binding Kinetics of MYL1501D and Lantus-US to IR-A (Short Form)

Drug	K_a(1Ms^{-1})[a]	K_d(1/s)[a]	K_D(nM)[a]
MYL1501D (Process VI)	1.245E to 1.146E+06 Ms^{-1}	0.024 to 0.030 s^{-1}	2.107E-08 to 2.407E-08 M
Lantus-US	1.187E to 1.645E+06 Ms^{-1}	0.022 to 0.031 s^{-1}	1.861E-08 to 2.320E-08 M

Abbreviations: Ka, Rate of association; kd, Rate of dissociation; KD, Equilibrium dissociation constant; US, United States
a: Average of N=3 reported

The binding kinetics observed were highly similar across multiple batches of MYL-1501D (process VI) and Lantus-US.

4.1.2 In Vitro Insulin Receptor Phosphorylation

The insulin receptor is a glycoprotein consist of two α-subunits and two transmembrane β-subunits. Insulin binding to the α-subunit induces autophosphorylation of the β-subunit cytoplasmic domain on multiple tyrosine residues, which activates the protein tyrosine kinase. The AlphaScreen® SureFire® assay, which detects the phosphorylated tyrosine 1150/1151 epitope, is used to measure the phosphorylation of endogenous (total) IR in cellular lysates of HepG2 cells (human hepatocellular carcinoma) stimulated with different doses of MYL-1501D, Lantus-US, or Lantus-EU. Potency is expressed relative to the activity of a working standard.

Total Insulin Receptor Phosphorylation Assays

Total IR phosphorylation induced by the insulin glargine was measured in lysates from hepatocellular carcinoma (HepG2) cells using the AlphaScreen® SureFire® p-Tyr1150/1151 assay.

Study BDL/SAR/BR.15.0003/16/001: Characterization of Insulin Glargine reference product (Lantus) sourced from EU and US region by in-vitro Functional Bioassays

Study BDL/TR/BR.15.0003/16/002: Report Title: Side by Side Comparability Assessment of Biocon's Insulin Glargine with EU and US Sourced Lantus® Reference Product by in-vitro Bioassays

IR phosphorylation was induced by different batches of MYL-1501D (Process V and Process VI), Lantus-US and Lantus-EU administered at 0, 8.4, 14.0, 23.3, 38.9, 64.8, 108, 180, 300, or 500 ng/mL. Phosphorylation was quantified as relative fluorescence and expressed as potency relative to the working standard relative potency was similar across batches of MYL-1501D (ranging from 0.91 to 1.14), and Lantus-US (ranging from 0.86 to1.18). and Lantus-EU (ranging from 0.86 to 1.16).

Table 16: Relative Potency of MYL-1501D, Lantus-US, and Lantus-EU Measured by Total Insulin Receptor Phosphorylation Assay

	MYL-1501D[a]	Lantus-US[b]	Lantus-EU[c]
Average relative potency (range)	0.91-1.14	0,86-1.18	0.86-1.16

Potency is expressed relative to that of the working standard
a: 15 batches were analyzed
b: 27 batches were analyzed
c: 22 batches were analyzed

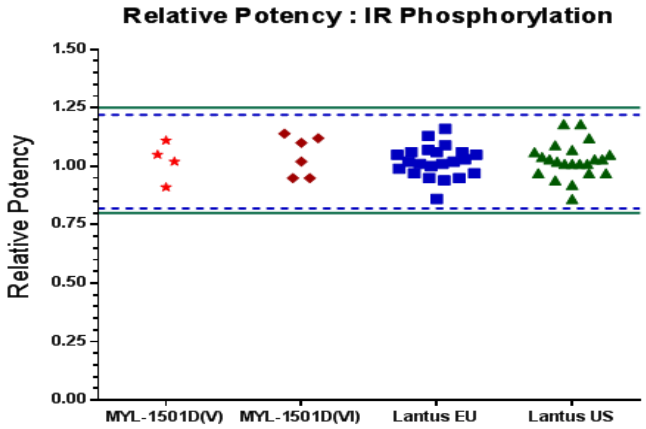


Figure 4: Relative Potency of Insulin Receptor Phosphorylation

Study CDL/TR/BR.15.0003/17/002

IR phosphorylation was induced by different batches of MYL-1501D (Process VI) and Lantus-US), expressed as potency relative to the working standard. Relative potency as similar across batches of MYL-1501D Process VI (ranging from 0.94 to1.13) and Lantus-US (ranging from 0.99 to 1.15).

Table 17: Comparative Activity of MYL-1501D (Process VI) and Lantus (US) Compared to Working Standard in Total Insulin Receptor Phosphorylation Assay

Drug	Total IR Phosphorylation-Relative Potency
MYL-1501D (Process VI)	0.94 to1.13
Lantus-US	0.99 to 1.15

Insulin Receptor-A Phosphorylation Assay

Phosphorylation of IR-A induced by the test articles was measured in CHO-K1 cell lysates using the AlphaScreen SureFire p-Tyr1150/1151 assay.

Studies: BDL/SAR/BR.15.0003/16/001 and BDL/TR/BR.15.0003/16/002:

In these studies, IR-A phosphorylation was induced by different batches of MYL-1501D (Processes V and VI), Lantus-US, and Lantus-EU administered at 0, 2.34, 4.69, 9.38, 18.75, 37.5, 75, 150, or 300 ng/mL. Phosphorylation was quantified as relative fluorescence and expressed as potency relative to the working standard QC/Q3/WSEP/006/05. Relative potency was similar across batches of MYL-1501D (ranging from 0.95 to 1.19), Lantus-US (ranging from 0.97 to 1.17), and Lantus-EU (ranging from 0.83 to 1.17).

Table 18: Comparative Activity of MYL-1501D and Lantus-US Compared to QC/Q3/WS-EP/006/05 Working Standard in Insulin Receptor Short Form (IR-A) Phosphorylation Assay

Drug	IR-A Phosphorylation-Relative Potency
MYL-1501D Process V and VI	0.95 to 1.19
Lantus-US	0.97 to 1.17

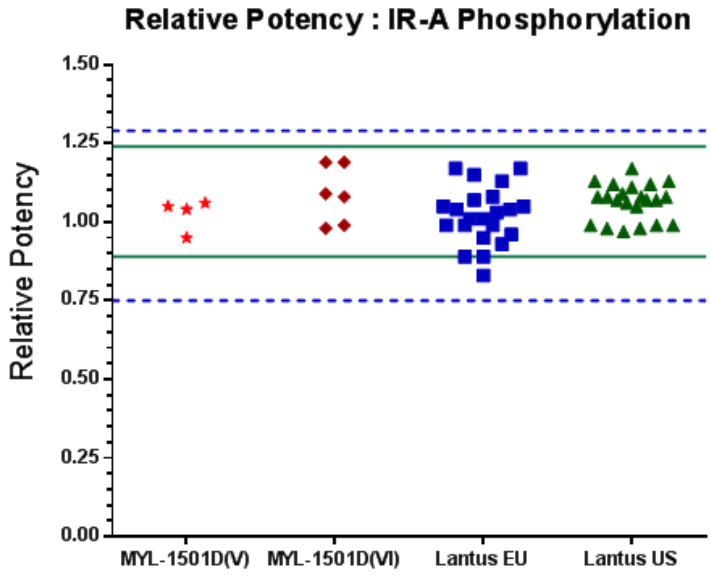


Figure 5: Relative Potency of IR-A Phosphorylation

Study CDL/TR/BR.15.0003/17/002

Phosphorylation of IR-A induced by the test articles was measured in CHO-K1 cell lysates using the AlphaScreen SureFire p-Tyr1150/1151 assay.

This study compared batches of MYL-1501D (Process VI) and Lantus-US. Relative potency was similar for batches of MYL-1501D (ranging from 0.92 to 1.12) and Lantus-US (ranging from 1.05 to 1.14).

Table 19: Comparative Activity of MYL-1501D and Lantus-US Compared to Working Standard in Insulin Receptor Short Form (IR-A) Phosphorylation Assay

Drug	IR-A Phosphorylation-Relative Potency
MYL-1501D Process VI	0.92 to 1.12
Lantus-US	1.05 to 1.14

Insulin Receptor-B Phosphorylation Assay

Phosphorylation of IR-B was measured in CHO-K1 cell lysates using the AlphaScreen SureFire p-Tyr1150/1151 assay.

Studies BDL/SAR/BR.15.0003/16/001 and BDL/TR/BR.15.0003/16/002
IR-B phosphorylation was induced by different batches of MYL-1501D (Processes V and VI) and Lantus (US and EU) administered at 0, 3.13, 6.25, 12.50, 25.00, 50.00, 100.00, 200.00, or 400.00 ng/mL, quantified as relative fluorescence and expressed as potency relative to the working standard. Relative potency was similar across batches of MYL-1501D (ranging from 0.97 to 1.18), and Lantus-US (ranging from 0.94 to 1.21).

Table 20: Comparative Activity of MYL-1501D and Lantus (US and EU) Compared to Working Standard in Insulin Receptor-B Phosphorylation Assay

Drug	IR-B Phosphorylation-Relative Potency
MYL-1501D Process V and VI	0.97 to 1.18
Lantus-US	0.94 to 1.21

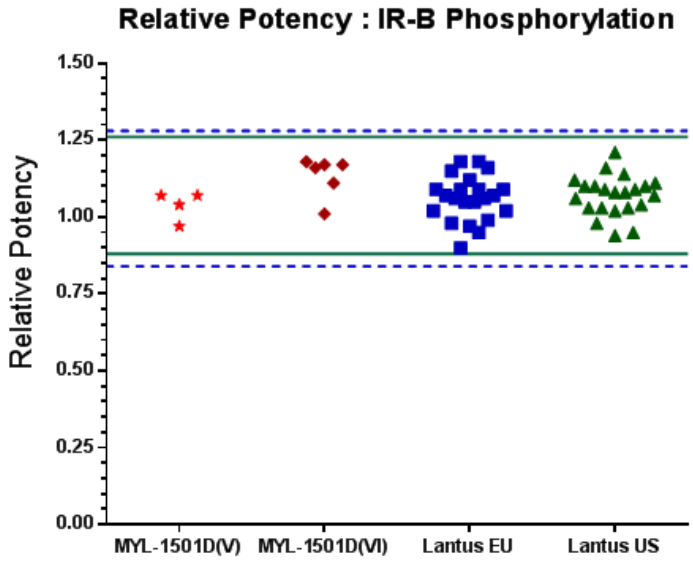


Figure 6: Relative Potency of IR-B Phosphorylation

Study CDL/TR/BR.15.0003/17/002

IR-B phosphorylation induced by different batches of the MYL-1501D (process VI) and Lantus-US, expressed as potency relative to the working standard is shown in Table 20. Relative potency was similar across batches of MYL-1501D Process VI (ranging from 0.87 to 1.07) and Lantus-US (ranging from 0.88 to 1.12).

Table 21: Comparative Activity of MYL-1501D and Lantus-US Compared to Working Standard in Insulin Receptor-B Phosphorylation Assay

Drug	IR-B Phosphorylation-Relative Potency
MYL-1501D Process VI	0.87 to 1.07
Lantus-US	0.88 to 1.12

4.1.3 Metabolic Potency

Enzymatic Glucose Uptake Assays for Evaluation of the Metabolic Activity of Lantus-US and MYL-1501D Formulations

MYL-1501D (Process V and Process VI) were compared with that of Lantus-US and Lantus-EU for glucose uptake in differentiated mouse 3T3-L1 adipocytes using the glucose oxidase/peroxidase assay. These drugs were administered at 0, 1.56, 3.13, 6.25, 12.5, 25, 50, 100, or 200 ng/mL. This assay measures residual glucose left in the medium using a colorimetric method. The uptake of glucose by adipocytes results in decrease of glucose content in the medium which can be measured using glucose oxidase peroxidase (GOPOD) reagent. The color change is proportional to the glucose

concentration and is measured by absorbance at 550 nm, using a spectrophotometer. Absorbance values were used to calculate potency relative to a working standard.

Study BDL/TR/BR.15.0003/16/002

The results of this study showed that relative potencies of MYL-1501D (Process VI), Lantus-US, and Lantus-EU, which are highly similar (values ranged from 0.90 to 1.06, 0.94 to 1.12, and 0.83 to 1.12, respectively).

Table 22: Comparative Activity of MYL-1501D and Lantus (US and EU) Compared to Standard in Metabolic Assay

Drug	Relative Metabolic Activity
MYL-1501D (Process V and VI)	0.90 to 1.06
Lantus-US	0.94 to 1.12

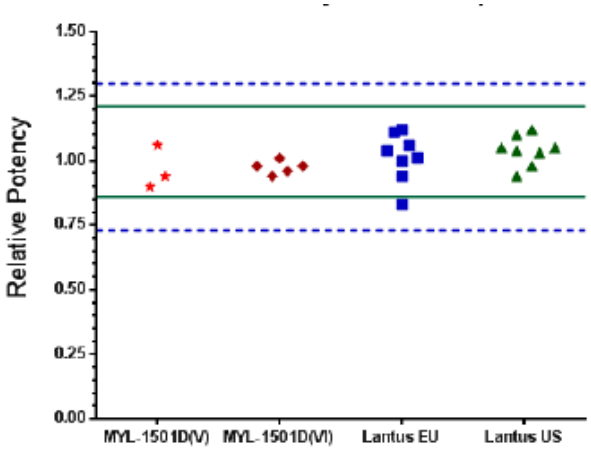


Figure 7: Relative Potency of Glucose Uptake

Study CDL/TR/BR.15.0003/17/002

In this study, the metabolic activity of MYL-1501D (process VI) batches was compared with that of Lantus-US batches. The relative potencies were similar for MYL-1501D Process VI (ranging from 0.92 to 1.16) and Lantus-US (ranging from 0.87 to 1.10).

Table 23: Comparative Activity of MYL-1501D and Lantus-US Compared to

Drug	Relative Metabolic Activity
MYL-1501D Process VI	0.92 to 1.16
Lantus-US	0.87 to 1.10

In summary, the pharmacodynamic parameters of the clinical formulation, MYL-1501D (Process VI) and the reference product, Lantus-US and Lantus-EU were compared in in vitro studies. The results demonstrate that MYL-1501D (Process VI) and Lantus-US have similar in vitro binding affinity for the IR, cause similar receptor phosphorylation, and are equipotent in in vitro metabolic assays.

4.2 In Vivo Pharmacodynamics

The only comparative pharmacodynamic evaluation of the to-be-marketed formulation, MYL-1501D (process VI) and Lantus-US was performed as part of a 28-day repeat-dose rat toxicity study. The primary objective of this study was to assess the potential toxicity of MYL-1501D Processes VI versus Lantus-US administered subcutaneously to Wistar rats once daily. Wistar rats were treated subcutaneously with 0, 0.08, 0.16, or 0.38 mg/kg MYL-1501D (process V), MYL-1501D (Process VI), or Lantus-US, and blood was collected from the retro-orbital plexus at time 0 (pre-dose), 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours from 3 rats per group per time point. Plasma was separated via centrifugation and glucose analysis was performed with a clinical chemistry analyzer. MYL-1501D (process V), MYL-1501D (process VI), or Lantus-US showed a similar time versus serum glucose concentration-response profile and exhibited a dose-dependent effect on serum glucose with similar magnitude and duration of effect at equivalent doses.

Details of this study are in Section 6.2 of this review.

4. 3 Secondary Pharmacology

4.3.1 In Vitro Binding to Insulin Growth Factor-1 Receptor

Studies BDL/SAR/BR.15.0003/16/001 and BDL/TR/BR.15.0003/16/002

The IGF-1R binding affinities of MYL-1501D, Lantus-US, and Lantus-EU were compared using surface plasmon resonance technology on the Biacore instrument platform in the kinetics mode.

As shown in Table 26, the mean values of triplicate measures for K_a, K_d, and K_D were similar for different batches of the 3 test articles. Mean K_a ranged from 1.53E+05 to 1.76E+05 Ms^{-1} for MYL-1501D, and 1.47E+05 to 1.96E+05 Ms^{-1} for Lantus-US. Mean K_d ranged from 0.0462 to 0.0513 s^{-1} for MYL-1501D, 0.0458 to 0.0542 s^{-1} for Lantus-US. Mean K_D ranged from 0.27 to 0.32 μM for MYL-1501D, 0.26 to 0.34 μM for Lantus-US, and 0.25 to 0.35 μM for Lantus-EU.

Table 24: Comparative Activity of MYL-1501D and Lantus (US and EU) in Insulin Growth Factor-1 Receptor Binding Kinetics Assay

Drug	$K_a(1Ms^{-1})^a$	$K_d(1/s)^a$	$K_D(uM)^a$
MYL1501D (Process VI)	1.53E+05 to 1.76E+05 Ms^{-1}	0.0462 to 0.0513 s^{-1}	0.27 to 0.32 μM
Lantus-US	1.47E+05 to 1.96E+05 Ms-1	0.0458 to 0.0542 s^{-1}	0.26 to 0.34 μM

Abbreviations: K_a, Rate of association; K_d, Rate of dissociation; K_D, Equilibrium dissociation constant; US, United States
a: Average of N=3 reported

4.4 Safety Pharmacology

The Applicant did not perform safety pharmacology studies with MYL-1501D and relies upon the safety pharmacology studies performed in mice, rats, guinea pigs, and dogs supporting approval of Lantus-US. The major safety pharmacology concern is related to drug-related induction of hypoglycemia.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The only comparative pharmacokinetic evaluation of the clinical formulation, MYL-1501D (Process VI) and MYL-1501D (Process V) and Lantus-US was performed as part of a 28-day repeat dose rat toxicity study. The primary objective of this study was to assess the potential toxicity of MYL-1501D (Process V) MYL-1501D (Process VI), and Lantus-US administered subcutaneously to Wistar rats daily. Pharmacokinetics was also assessed in this study.

Wistar rats were treated subcutaneously with 0, 0.08, 0.16, or 0.38 mg/kg MYL-1501D (Process V), MYL-1501D (Process VI), or Lantus-US, and blood was collected from the retro-orbital plexus at time 0 (pre-dose), 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours from 3 rats per group per time point. Plasma was separated via centrifugation and pharmacokinetic analysis was performed. MYL-1501D (Process V), MYL-1501D (Process VI), or Lantus-US showed similar pharmacokinetic parameters. Details of this study is in Section 6.2.1 of this review.

5.2 Pharmacokinetics Drug Interactions

Applicant did not perform any nonclinical drug-drug interactions studies, but instead relies on the information described in Lantus-US labeling, which includes medications

that may potentiate as well as medications that may reduce the blood glucose-lowering effect of Lantus-US.

6 General Toxicology

6.1 Single-Dose Toxicity

No comparative single dose toxicity study was performed with the clinical formulation of MYL-1501D (process VI) and Lantus-US and hence these studies are not reviewed.

6.2 Repeat-Dose Toxicity

Study: Comparative 28-Day Toxicity Study of Insulin Glargine (rDNA origin) from Process 5 and Insulin Glargine (rDNA origin) from Process 6 with Reference Product (Lantus® SoloStar®) [Lantus-US] by Subcutaneous Route in Wistar Rats

Study no.:	U-16176
Study report location:	SDN1, SN0000
Conducting laboratory and location:	(b) (4)
Date of study initiation:	23 Sep 2016
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MYL-1501D (rDNA origin) Process V; Lot # BS15005851 MYL-1501D (rDNA origin) Process VI Lot # BS15009376 Lantus® SoloStar® [Lantus-US] Lot # 4F655A

Key Study Findings

- MYL-1501D (rDNA origin) from process V versus MYL-1501D from Process VI and Lantus-US were administered to rats at 0.08, 0.16 or 0.38 mg/kg once daily by the subcutaneous route for 4 weeks, followed by a 14-week treatment-free recovery period.

- There were no significant differences noted between MYL-1501D (Process VI) and Lantus-US for any of the endpoints assessed in this 4-week comparative study.

Methods

Doses:	0.38, 0.16, 0.08 mg/kg/day
Frequency of dosing:	Once-daily

Route of administration: Subcutaneous injection
Dose volume: 2.5 mL/kg
Formulation/Vehicle: Vehicle represents the final formulation composition of the test items and reference item and consisted of following excipients

Ingredients	Quantity
m-Cresol	2.65 mg (80 -
Zinc content	(b) (4) µg/100 IU (Not
Hydrochloric	For pH
Sodium	For pH
Water for	Qs

Species/Strain: Rat (*Rattus norvegicus*) Wistar
Number/Sex/Group: Main and recovery groups: 10 /sex/group
Age: 49 to 56 days (7 - 8 weeks)
Weight: Males: 166.48 to 242.58g: Females: 130.95 to 170.21 g
Satellite groups: Toxicokinetics: 9/sex/group except vehicle control
Unique study design: TK which contained 3 males and 3 females and Process 6 toxicokinetic group contained 10 males and 9 females.
Deviation from study protocol: The protocol deviations were noted in the GLP Compliance Statement. These deviations were not considered to have significant impact on integrity of the study.

Study Design

Table 25: Repeat-Dose Toxicity Study Design-Main Group

Group No.	Group	Dose mg/kg/day (IU/kg/day)	Dose conc. mg/mL (IU/mL)	No. of Rats		Rat Number	
				Males	Females	Males	Females
G1	Vehicle Control	0	0	10	10	Rb1980 to Rb1989	Rb2204 to Rb2213
G2a	Low Dose - Test item 1	0.08 (2.20)	0.032 (0.88)	10	10	Rb1990 to Rb1999	Rb2214 to Rb2223
G2b	Low Dose - Test item 2	0.08 (2.20)	0.032 (0.88)	10	10	Rb2000 to Rb2009	Rb2224 to Rb2233
G2c	Low Dose - Reference Item	0.08 (2.20)	0.032 (0.88)	10	10	Rb2010 to Rb2019	Rb2234 to Rb2243
G3a	Mid Dose - Test item 1	0.16 (4.40)	0.064 (1.76)	10	10	Rb2020 to Rb2029	Rb2244 to Rb2253
G3b	Mid Dose - Test item 2	0.16 (4.40)	0.064 (1.76)	10	10	Rb2030 to Rb2039	Rb2254 to Rb2263
G3c	Mid Dose - Reference item	0.16 (4.40)	0.064 (1.76)	10	10	Rb2040 to Rb2049	Rb2264 to Rb2273
G4a	High Dose - Test item 1	0.38 (10.45)	0.152 (4.18)	10	10	Rb2050 to Rb2059	Rb2274 to Rb2283
G4b	High Dose - Test item 2	0.38 (10.45)	0.152 (4.18)	10	10	Rb2060 to Rb2069	Rb2284 to Rb2293
G4c	High Dose - Reference item	0.38 (10.45)	0.152 (4.18)	10	10	Rb2070 to Rb2079	Rb2294 to Rb2303

Table 26: Repeat-Dose Toxicity Study Design-Recovery groups

Group No.	Group	Dose mg/kg/day (IU/kg/day)	Dose conc. mg/mL (IU/mL)	No. of Rats		Rat Number	
				Males	Females	Males	Females
G1R	Vehicle Control Recovery	0	0	10	10	Rb2080 to Rb2089	Rb2304 to Rb2313
G4aR	High Dose Recovery - Test item 1	0.38 (10.45)	0.152 (4.18)	10	10	Rb2090 to Rb2099	Rb2314 to Rb2323
G4bR	High Dose Recovery - Test item 2	0.38 (10.45)	0.152 (4.18)	10	10	Rb2100 to Rb2109	Rb2324 to Rb2333
G4cR	High Dose Recovery - Reference item	0.38 (10.45)	0.152 (4.18)	10	10	Rb2110 to Rb2119	Rb2334 to Rb2343

Note: TK: Toxicokinetics, Test Item 1: MYL-1501D (rDNA origin) Process 5; Test Item 2: MYL-1501D (rDNA origin) Process 6, Reference Item: Lantus-US, 100 IU = 3.6378 mg

"a" , "b" and "c" in the group number indicates treatment with MYL-1501D (rDNA origin) Process 5, MYL-1501D (rDNA origin) Process 6 and Lantus-US, respectively.

Observations and Results

Dose Confirmation analysis

The formulations prepared for day 1 and day 28 dosing was analyzed for their concentrations and found to be within acceptance limits (% recovery: 100 ± 10%).

Table 27: Dose Confirmation Analysis Results

Date		Insulin Glargine (rDNA origin) from Process 5			Insulin Glargine (rDNA origin) from Process 6			Lantus® SoloStar®		
		Low	Mid	High	Low	Mid	High	Low	Mid	High
29-Sep-16 (prepared for day 1 dosing)	% Recovery	98.44	109.38	101.97	90.63	103.13	104.94	104.69	109.38	109.54
	SD	2.21	0	0	0	0	0.46	2.21	0	0.47
	% RSD	2.2	0	0	0	0	0.4	2.1	0	0.4
26-Oct-16 (prepared for day 28 dosing)	% Recovery	90.63	98.44	103.95	96.88	101.56	104.61	96.88	98.44	107.89
	SD	0	0	0	0	0	1.93	0	0	0
	% RSD	0	0	0	0	0	0.9	0	0	0

Note: No Insulin Glargine concentration was found in placebo samples during all dose confirmation analysis.

Mortality

Two male rats (one in TK group and one in main group) died at the highest dose (0.38 mg/kg/day) of insulin glargine (Process VI). One TK rat died on day 1 at approximately 3 hours post-dose and one main group rat died on day 4 at approximately 6-hour post dose. The cause of death is attributed to exaggerated pharmacodynamics effect (i.e., hypoglycemia) based on the glucose values prior to death. No other mortality was

observed in insulin glargine (Process VI), insulin glargine (Process V) or Lantus-US treated rats.

The incidence of mortality at the high dose due to exaggerated pharmacodynamic effects in the males was low (2/19 rats) and there was no mortality in the females. This could be due to higher potency of MYL-1501D (Process VI) compared to Lantus-US or due to inter-animal variability of the animals used in this study. The minimum glucose levels (Rmin) on day 1 and day 28 in MYL-1501D (Process VI) (male: 62.81 – 72.98 mg/dL, female: 68.73 - 71.12 mg/dL) was comparable to Lantus-US (male: 61.92 – 83.73 mg/dL, female: 63.10 – 83.19 mg/dL). This observation indicated the pharmacodynamic effects of MYL-1501D (Process VI) are similar to Lantus-US and it is highly unlikely that the mortality is due to the differences in the potencies.

Table 28: Summary of Mortality and Clinical Signs – Male Rats

Group No.	G1/ G1R/ G1TK	G2a/ G2aTK	G2b/ G2bTK	G2c/ G2cTK	G3a/ G3aTK	G3b/ G3bTK	G3c/ G3cTK	G4a/ G4aR/ G4aTK	G4b/ G4bR/ G4bTK#	G4c/ G4cR/ G4cTK
Dose (mg/kg/day)	**0**	**0.08**	**0.08**	**0.08**	**0.16**	**0.16**	**0.16**	**0.38**	**0.38**	**0.38**
No. of rats	**23**	**19**	**19**	**19**	**19**	**19**	**19**	**29**	**30**	**29**
Mortality	0	0	0	0	0	0	0	0	2	0
Clinical Signs										
Normal	21	17	18	17	19	19	18	29	27	28
Scab, dorsal thoracic	2	2	1	2	0	0	1	0	1	0
Tremors and Lateral recumbency	0	0	0	0	0	0	0	0	1	0
Cold to touch and Sternal recumbency	0	0	0	0	0	0	0	0	1	0
Snuffles	0	0	0	0	0	0	0	0	0	1

#: Two mortalities observed (Rb2186 and Rb2068) at 0.38 mg/kg/day dose of Insulin Glargine (rDNA origin) Process 6. The blood glucose measured for both rats prior to death on day 1 using glucometer showed value below detection limit (i.e. <20 mg/dL).
"a", "b" and "c" in the group No. indicates treatment with Insulin Glargine (rDNA origin) Process 5, Insulin Glargine (rDNA origin) Process 6 and Lantus® SoloStar®, respectively.

Table 29: Summary of Mortality and Clinical Signs – Female Rats

Group No.	G1/ G1R/ G1TK	G2a/ G2aTK	G2b/ G2bTK	G2c/ G2cTK	G3a/ G3aTK	G3b/ G3bTK	G3c/ G3cTK	G4a/ G4aR/ G4aTK	G4b/ G4bR/ G4bTK	G4c/ G4cR/ G4cTK
Dose (mg/kg/day)	0	0.08	0.08	0.08	0.16	0.16	0.16	0.38	0.38	0.38
No. of rats	23	19	19	19	19	19	19	29	29	29
Mortality	0	0	0	0	0	0	0	0	0	0
Clinical Signs										
Normal	23	18	19	19	19	18	18	27	29	28
Scab, dorsal thoracic	0	1	0	0	0	0	0	1	0	1
Injury, right eye, mild and Corneal opacity, right eye, mild	0	0	0	0	0	1	0	0	0	0
Injury, right eye, moderate and Eyelids closed, right eye	0	0	0	0	0	0	1	0	0	0
Corneal opacity, right eye, mild and Ulcer, cornea right eye, mild	0	0	0	0	0	0	0	1	0	0

"a", "b" and "c" in the group No. indicates treatment with Insulin Glargine (rDNA origin) Process 5, Insulin Glargine (rDNA origin) Process 6 and Lantus® SoloStar®, respectively.

Of the two rats observed dead, one rat (No. Rb2186) showed clinical signs of tremors and lateral recumbency at approximately 3 hours post dose on day 1. The blood glucose measured prior to death on day 1 using glucometer showed value below detection limit (i.e., <20 mg/dL), while the other rat (Rat No. Rb2068) showed clinical signs of sternal recumbency and cold to touch at approximately 3 hours post dose on day 4. The blood glucose measured at 3 hour and prior to death (approximately 6 hours) on day 4 using glucometer showed value below detection limit (i.e., <20 mg/dL). The gross pathology examination of rat No. Rb2068 revealed red discoloration at subcutis (injection site 1, 2). Based on glucose values measured prior to death, the cause of death is attributed to exaggerated pharmacodynamic effect (i.e., hypoglycemia).

Clinical Signs

Scab formation at injection site was randomly observed during the treatment period in a few animals of all treated groups including vehicle control group, and was related to the low pH of the formulation and injection procedure-related injury.

Table 30: Local injection site related signs

Treatment	Placebo	Process 5			Process 6			Lantus® SoloStar®		
Dose (mg/kg/day)	0	0.08	0.16	0.38	0.08	0.16	0.38	0.08	0.16	0.38
Males										
Scab, dorsal thoracic	2/23	2/19	-	-	1/19	-	1/30	2/19	1/19	-
Females										
Scab, dorsal thoracic	-	1/19	-	1/29	-	-	-	-	-	1/29

Process 5: MYL-1501D from Process V, Process 6: MYL-1501D from Process VI

Table 31: Summary of Detailed Clinical Examination – Male Rats

Day	Group No.	G1/ G1R	G2a	G2b	G2c	G3a	G3b	G3c	G4a/ G4aR	G4b/ G4bR	G4c/ G4cR
	Dose (mg/kg/day)	0	0.08	0.08	0.08	0.16	0.16	0.16	0.38	0.38	0.38
-1	Normal	20	10	10	10	10	10	10	20	20	20
	No. of rats examined	20	10	10	10	10	10	10	20	20	20
8	Normal	20	10	10	10	10	10	10	20	19	20
	No. of rats examined	20	10	10	10	10	10	10	20	19	20
15	Normal	20	10	10	10	10	10	10	20	19	20
	No. of rats examined	20	10	10	10	10	10	10	20	19	20
22	Normal	20	10	10	10	10	10	10	20	19	20
	No. of rats examined	20	10	10	10	10	10	10	20	19	20
28	Normal	18	8	9	8	10	10	9	20	19	20
	Scab, dorsal thoracic	2	2	1	2	0	0	1	0	0	0
	No. of rats examined	20	10	10	10	10	10	10	20	19	20
35	Normal	10	-	-	-	-	-	-	10	10	10
	No. of rats examined	10	-	-	-	-	-	-	10	10	10
42	Normal	10	-	-	-	-	-	-	10	10	10
	No. of rats examined	10	-	-	-	-	-	-	10	10	10

"a", "b" and "c" in the group No. indicates treatment with Insulin Glargine (rDNA origin) Process 5, Insulin Glargine (rDNA origin) Process 6 and Lantus® SoloStar®, respectively.

Table 32: Summary of Detailed Clinical Examination – Female Rats

Day	Group No.	G1/ G1R	G2a	G2b	G2c	G3a	G3b	G3c	G4a/ G4aR	G4b/ G4bR	G4c/ G4cR
	Dose (mg/kg/day)	0	0.08	0.08	0.08	0.16	0.16	0.16	0.38	0.38	0.38
-1	Normal	20	10	10	10	10	10	10	20	20	20
	No. of rats examined	20	10	10	10	10	10	10	20	20	20
8	Normal	20	10	10	10	10	10	10	20	20	20
	No. of rats examined	20	10	10	10	10	10	10	20	20	20
15	Normal	20	10	10	10	10	10	10	20	20	20
	No. of rats examined	20	10	10	10	10	10	10	20	20	20
22	Normal	20	10	10	10	10	10	10	20	20	20
	No. of rats examined	20	10	10	10	10	10	10	20	20	20
28	Normal	20	9	10	10	10	10	10	18	20	19
	Scab, dorsal thoracic	0	1	0	0	0	0	0	1	0	1
	Ulcer, cornea, mild right eye	0	0	0	0	0	0	0	1	0	0
	No. of rats examined	20	10	10	10	10	10	10	20	20	20
35	Normal	10	-	-	-	-	-	-	10	10	10
	No. of rats examined	10	-	-	-	-	-	-	10	10	10
42	Normal	10	-	-	-	-	-	-	10	10	10
	No. of rats examined	10	-	-	-	-	-	-	10	10	10

"a", "b" and "c" in the group No. indicates treatment with Insulin Glargine (rDNA origin) Process 5, Insulin Glargine (rDNA origin) Process 6 and Lantus® SoloStar®, respectively.

Treatment-related clinical signs such as tremor, lateral recumbency, sternal recumbency and being cold to touch were observed in the two at 0.38 mg/kg/day dose of MYL-1501D (Process VI), prior to their death. These clinical signs are related to test articles and the deaths were attributed to exaggerated pharmacodynamics effect (hypoglycemia) of test item. The minimum glucose levels (Rmin) on day 1 and day 28 in MYL-1501D (Process VI) (male: 62.81 – 72.98 mg/dL, female: 68.73 - 71.12 mg/dL) was comparable to Lantus-US (male: 61.92 – 83.73 mg/dL, female: 63.10 – 83.19 mg/dL). This observation indicated the pharmacodynamic effects of MYL-1501D

(Process VI) are similar to Lantus-US and it is highly unlikely that the mortality and the clinical signs are due to the differences in the potencies.

One male rat from Lantus-US high dose group (showed clinical sign of snuffles during days 16-17 of treatment, which was recovered and not observed from day 18. Blood sampling procedure related ocular clinical signs were observed in one main group female and two TK female rats. Clinical signs such as mild eye injury and mild corneal opacity in one Process VI TK mid dose female, moderate eye injury and eyelids closed in one Lantus-US TK mid dose female and mild corneal opacity and mild corneal ulcer in Process V high dose female were observed during treatment period.

Snuffle observed in one male rat was considered as incidental finding. The ocular clinical signs observed in females were mostly attributed to blood sampling from retro-orbital plexus during day 1 toxicokinetics and not considered test items or reference item related.

Ophthalmological Examination

No abnormalities related to the treatment of MYL-1501D (Process VI), MYL-1501D (Process V) or Lantus-US were found in the eyes during week 4 of treatment period. Mild corneal opacity observed in one female from MYL-1501D V group was not considered as test item related finding.

Table 33: Summary of Ophthalmological Examination – Female Rats

Group No. Dose (mg/kg/day)	No. of rats examined	Observation	Week 4 (Day 26)
G1 0	10	NAD	10
G4a 0.38	10	NAD	9
		Corneal opacity, right eye, mild	1
G4b 0.38	10	NAD	10
G4c 0.38	10	NAD	10

NAD: No abnormality detected. ^: Ophthalmological examination not performed in low, mid and recovery groups because no treatment related eye abnormalities were observed in high dose groups.
Note: Ophthalmological examinations performed in all animals using an ophthalmoscope once during acclimatization period did not reveal abnormality.
"a", "b" and "c" in the group No. indicates treatment with Insulin Glargine (rDNA origin) Process 5, Insulin Glargine (rDNA origin) Process 6 and Lantus® SoloStar®, respectively.

Functional Observational Battery and Motor Activity

Insulin glargine-related decrease in distance travelled (male: 31-38%, female: 23- 36%), horizontal count (male: 35-45%, female: 30-41%), ambulatory count (male: 43-48%, female: 41-44%) and vertical count (male: 30-32%, female: 22-38%) were observed at 0.38 mg/kg/day dose of Process V, Process VI and Lantus-US as compared to vehicle control. The motor activity evaluation was done approximately one hour post dose in week 4, and the decrease in motor activity parameters are likely related to the hypoglycemia. There were no statistical changes observed in motor activity parameters at 0.08 and 0.16 mg/kg/day doses during week 4 of treatment and in recovery groups during recovery period.

Body Weight and Body Weight Gain

No MYL-1501D (Process VI), MYL-1501D (Process V) or Lantus-US-related changes were observed in body weight and body weight gain in treated males and females as compared to vehicle control. However, the body weight gain was significantly lower on days 15-22 in Lantus-US-treated females assigned to low (0.08 mg/kg/day) dose (8.44 g) as compared to vehicle control or vehicle control recovery group (14.26 g). The corresponding changes in mean body weight were minimal (3%) during same interval and there were no significant changes further until end of study. Therefore, the minimal decrease in body weight gain was not considered treatment-related.

Food Consumption

There was no difference in food consumption between MYL-1501D (Process VI) and Lantus-US-treated male and female rats.

Hematology, Clinical Chemistry and Urinalysis

No MYL-1501D (Process VI), MYL-1501D (Process V) or Lantus-US-related changes were observed in hematology, clinical chemistry and urinalysis parameters evaluated on day 29 (i.e., 24 hours after last dose) and on day 43 in treated males and females as compared to vehicle control.

Gross pathology

MYL-1501D (Process VI), MYL-1501D (Process V) or Lantus-US-related gross lesions were not observed in the treated groups. Red discoloration at the injection site was observed in all treated groups including vehicle control group. Scab formation was noted in a similar number of rats across all groups except at 0.16 mg/kg/day dose of Process V. However, there was no dose related trend observed grossly. The gross changes at injection site were completely recovered at the end of recovery period in both sexes. Other gross changes were randomly distributed across the groups and were considered as spontaneous findings.

Table 34: Gross changes observed across all the groups including vehicle treated group, at the injection sites

Gross Lesions	Group No., Dose (mg/kg/day) and No. of animals									
	Sex	G1	G2a	G2b	G2c	G3a	G3b	G3c	G4a	G4b	G4c
		0	0.08	0.08	0.08	0.16	0.16	0.16	0.38	0.38	0.38
		10	10	10	10	10	10	10	10	10	10
Sub cutis - discoloration, red	M	10	9	8	10	10	9	9	10	10	9
	F	10	9	9	9	9	8	10	10	8	6
Scab formation	M	2	4	0	2	0	0	2	1	1	0
	F	0	1	1	2	0	1	1	1	1	2
Subcutaneous-focus, white	M	0	0	0	0	1	0	0	0	0	0

M: Male, F: Female, "a", "b" and "c" in the group No. indicates treatment with Insulin Glargine (rDNA origin) Process 5, Insulin Glargine (rDNA origin) Process 6 and Lantus® SoloStar®.

Organ Weight and Organ Weight Ratio

Generally, no MYL-1501D (Process VI), MYL-1501D (Process V) or Lantus-US-related changes were observed in organ weights in treated groups as compared to vehicle control.

A slight decrease in thyroid with parathyroid weights was observed in high dose female rats and are summarized in the table below. These changes in the thyroid weights for the rats treated with MYL-1501D (process VI) were similar to the ones treated with Lantus-US.

Table 35: Thyroid weights in high dose females

Sex	Female		
Group No.	G4a	G4b	G4c
Group	Insulin Glargine (rDNA origin) Process 5	Insulin Glargine (rDNA origin) Process 6	Lantus® SoloStar®
Dose (mg/kg)	0.38	0.38	0.38
No. of rats	10	10	10
Thyroid with parathyroids			
Absolute wt.	↓11%	↓19 %*	↓22 %*
Relative to Body wt.	↓7 %	↓14 %*	↓21 %*
Relative to Brain wt.	↓13 %	↓19 %*	↓23 %*

*Statistically significant;,↓: Decrease compared to vehicle control

The statistically significant changes in thyroid with parathyroid weights had normalized and were no longer different at the end of recovery period in female rats. The microscopic evaluation of thyroid with parathyroid in female rats revealed normal architecture of the glands and there was no correlation with any other sign of toxicity. Therefore, this slight change in thyroid with parathyroid weights in all three insulins

treated high dose female rats was not considered to bear toxicological significance and was not considered an adverse effect in calculating NOAEL.

There were no any other statistically significant changes in any of the organs weighed in both the sexes in all the treated groups including recovery groups.

Histopathology

The observations included minimal to mild inflammation and hemorrhages in the subcutaneous region and few incidences of minimal to mild epidermal crust formation, epidermal hyperplasia and epidermal erosion/ ulcers at the injection site. The minimal to mild inflammation was characterized by infiltration of macrophages, lymphocytes with occasional degeneration/regeneration of panniculus muscle. These changes were limited to the injection site without affecting the surrounding area. The incidence of these observations was similar among MYL-1501D (Process VI) and Lantus-US treated rats. The changes at injection sites were completely recovered at the end of 14-day treatment free period in both male and female rats. All other gross changes were randomly distributed across the groups and were considered as spontaneous findings.

Adequate Battery: Yes
Peer Review Histological Findings: Yes

Table 36: Histopathology Findings (Injection site reactions)

Microscopic Lesions	Sex	Group No., Dose (mg/kg/day) and No. of animals									
		G1	G2a	G2b	G2c	G3a	G3b	G3c	G4a	G4b	G4c
		0	0.08	0.08	0.08	0.16	0.16	0.16	0.38	0.38	0.38
		10	10	10	10	10	10	10	10	10	10
Epidermal crust	M	2	4	4	3	2	4	3	2	3	2
	F	2	1	1	4	2	4	3	2	2	3
Hemorrhage	M	10	10	9	10	10	9	10	10	10	9
	F	10	9	10	9	9	7	10	10	9	6
Inflammation	M	10	10	9	10	10	9	10	10	10	10
	F	10	8	10	9	6	7	9	10	8	7
Epidermal hyperplasia	M	1	3	4	3	2	5	3	4	3	2
	F	2	1	2	4	1	4	3	2	2	1
Epidermal erosion/ ulcer	M	0	0	0	0	0	0	0	1	0	1
	F	0	0	1	1	0	1	0	1	0	1

"a", "b" and "c" in the group No. indicates treatment with Insulin Glargine (rDNA origin) Process 5, Insulin Glargine (rDNA origin) Process 6 and Lantus® SoloStar®, respectively.

Plasma Glucose Pharmacodynamics Profile

Dose-related reductions in plasma glucose observed were consistent with primary pharmacological effect. The overall pattern of glucose reductions of MYL-1501D (Process V) and MYL-1501D (Process VI) was comparable with Lantus-US on Days 1 and 28. The minimum observed glucose value (Rmin) ratios among MYL-1501D (Process V) and MYL-1501D (Process VI) and Lantus-US were comparable on all

occasions. Other pharmacodynamics parameters such as the time corresponding to minimum glucose (Tmin), duration of effect (Time Below baseline) and glucose area below baseline ratios among MYL-1501D (Process V) and MYL-1501D (Process VI) and Lantus-US were also found to be comparable with ≤2-fold variation on most occasions. Therefore, the pharmacodynamics profile of MYL-1501D (Process V) and MYL-1501D (Process VI) and Lantus-US are considered comparable with each other. The pharmacodynamic effects of Myl-1501D (Process VI) and Lantus-US were similar in rats in this 28-day study.

DISCUSSION

A comparative 28-day repeat dose toxicity study in Wistar rats with daily subcutaneous treatment at 0.38, 0.16, 0.08 mg/kg/day of MYL-1501D (Process VI) and Lantus-US was performed to establish their comparability. Two male rats died at the highest dose (0.38 mg/kg/day) of insulin glargine (Process VI) groups. One rat died on day 1 at approximately 3 hours post-dose and the other died on day 4 at approximately 6-hour post dose. Treatment-related clinical signs such as tremor, lateral recumbency, sternal recumbency and being cold to touch were observed in the two at 0.38 mg/kg/day dose of MYL-1501D (Process VI), prior to their death. These clinical signs are related to test articles and the deaths were attributed to exaggerated pharmacodynamics effect (hypoglycemia) of the drug. No drug-related changes were observed in ophthalmological examination, functional observational battery, body weight, food consumption, hematology, clinical chemistry (24 hours post last dose) and urinalysis. Comparable MYL-1501D (Process VI) and Lantus-US-related decreased motor activity parameters were observed at 0.38 mg/kg/day dose. The mortalities were due to exaggerated pharmacodynamic effects (hypoglycemia) of Insulin Glargine. The degree and duration of hypoglycemia was comparable at each dose of MYL-1501D (Process VI) and Lantus-US. NOEL based on glucose reduction was <0.08 mg/kg/day in males and females. Therefore, the systemic toxicity profile of MYL-1501D (Process VI) was considered comparable with Lantus-US.

Scab formation at injection site was randomly observed during the treatment period in a few animals of all treated groups including vehicle control group. These findings were attributed to the low pH of the formulation and repeated subcutaneous injections for 28 days. The changes were independent of dose and were comparable among MYL-1501D (Process VI) and Lantus-US treated rats.

Dose-related reduction in plasma glucose observed was consistent with primary pharmacological effect. The overall pattern of glucose reduction of MYL-1501D (Process VI) was comparable with Lantus-US on days 1 and 28. The minimum observed glucose value (R_{min}) ratios among MYL-1501D (Process VI) and Lantus-US were comparable on all occasions. Other pharmacodynamics parameters such as the time corresponding to minimum glucose (T_{min}), duration of effect (Time Below baseline) and glucose area below baseline ratios among MYL-1501D (Process VI) and Lantus-US were also found to be comparable with ≤2-fold variation on most occasions. Therefore,

the pharmacodynamics profile of MYL-1501D (Process VI) and Lantus-US are considered comparable with each other.

CONCLUSIONS

Based on the results of the 28-day repeat dose comparative toxicity study in Wistar rats, the No Observed Adverse Effect Level (NOAEL) for MYL-1501D (Process VI) and Lantus-US was 0.16 mg/kg/day in males and > 0.38 mg/kg/day in females which is approximately 4 times and 10 times of the proposed therapeutic starting dose in humans (10 IU/day) based on body surface area. Except for the anticipated pharmacological effect of hypoglycemia, no other systemic effect was observed. The local and systemic changes observed during treatment were recovered at the end of the 14-day recovery period. MYL-1501D (Process VI) is considered to have similar systemic toxicity, local tolerance and pharmacodynamic profile as compared with Lantus-US.

7 Genetic Toxicology

Applicant has not performed any Genetic Toxicology study with MYL-1501D and relies on the Genetic Toxicology information referenced in Lantus-US label.

8 Carcinogenicity

Applicant has not performed any Carcinogenicity study with MYL-1501D and relies on the Carcinogenicity information referenced in Lantus-US label.

9 Reproductive and Developmental Toxicology

Applicant has not performed any Reproductive and Developmental Toxicology studies with MYL-1501D and relies on the Reproductive and Developmental Toxicology information referenced in Lantus-US label.

10 Special Toxicology Studies

Applicant has not performed any carcinogenicity study with MYL-1501D and relies on the carcinogenicity information referenced in Lantus-US label.

11 Integrated Summary

The Applicant, Mylan GmbH is seeking approval of Insulin Glargine Injection (code-name ‘MYL-1501D’), a recombinant human basal insulin, for the treatment of patients with diabetes mellitus. The Applicant seeks to rely, in part, on prior approval of the U.S. listed drug Lantus (Lantus-US) via the 505(b)(2) regulatory pathway. MYL-1501D shares the amino acid sequence with Lantus-US, but unlike Lantus-US that is produced

in *E. coli*, MYL-1501D is produced in *Pichia pastoris*. The to-be-marketed formulation of contains insulin glargine drug substance manufactured in Malaysia (MYL-1501D Process VI). The excipients and composition of MYL-1501D Processes VI are similar to those used in the listed drug (Lantus-US). MYL-1501D drug product (DP) (vials) batches manufactured by Biocon Sdn. Bhd. (Johor, Malaysia) were analyzed and found to comply with USP monograph of "Insulin Glargine Injection".

The probable product-related impurities formed due to the inherent nature of the (b) (4) (b) (4) MYL-1501D drug substance (DS). There is a very low level of concern regarding the safety of insulin product derived breakdown products.

MYL-1501D, like Lantus-US, is presented in both pre-filled pens and vials. MYL-1501D is administered either via a disposable, variable-dose, multiple-dose pen injector intended for self-administration via subcutaneous injection or from a vial via a standard insulin syringe. MYL-1501D for the pen presentation is formulated in a glass cartridge, while a pen injector device delivers the formulation. Based on the results obtained from the extractable, screening leachable and formal leachable studies, the chosen container closure system (glass cartridge, rubber plunger and (b) (4) rubber seal) is compatible with MYL-1501D. CDRH reviewed the Pre-Filled Pen at the request of CDER, and noted the biocompatibility information provided by the applicant to evaluate cytotoxicity, sensitization, and irritation endpoints of the user contact is appropriate and acceptable for the intended use of the user contacting of the combination product.

Comparative in vitro Potency Studies

Applicant conducted comparative studies to establish similarity between MYL-1501D Processes VI and the listed drug, Lantus-US. The in vitro insulin binding studies with insulin receptor long form (IR-B) and insulin receptor short form(IR-A) showed similar binding kinetics between MYL-1501D Processes VI and the listed drug, Lantus-US. similarly, measurement of IR phosphorylation induced by MYL-1501D Processes VI and the listed drug, Lantus-US in lysates from hepatocellular carcinoma (HepG2) showed similar total phosphorylation. When Phosphorylation of IR-A and IR-B induced by MYL-1501D Processes VI and the listed drug, Lantus-US was measured in CHO-K1 cell lysates, the relative potencies of phosphorylation were similar. MYL-1501D (Process VI) were compared with that of Lantus-US and Lantus-EU for glucose uptake in differentiated mouse 3T3-L1 adipocytes using the glucose oxidase/peroxidase assay. The results of this study showed that relative potencies of MYL-1501D (Process VI), and Lantus-US are highly similar.

***Comparative in vivo* Pharmacodynamics**

The only comparative pharmacodynamic evaluation of the MYL-1501D (process VI) and Lantus-US was performed as part of a 28-day repeat-dose rat toxicity study. The primary objective of this study was to assess the potential toxicity of MYL-1501D Processes VI versus Lantus-US administered subcutaneously at 0, 0.08, 0.16, or 0.38 mg/kg doses to Wistar rats once daily. The blood was collected at time 0 (pre-dose), 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours from 3 rats per group and glucose analysis was performed. MYL-1501D (process VI), or Lantus-US showed a similar time versus serum glucose concentration-response profile and exhibited a dose-dependent effect on serum glucose with similar magnitude and duration of effect at equivalent doses.

Secondary Pharmacology

Insulin Growth Factor-1 Receptor binding affinities of MYL-1501D (process VI), and Lantus-US were compared using surface plasmon resonance technology on the Biacore instrument platform in the kinetics mode. The mean values of triplicate measures for K_a, K_d, and K_D were similar for different batches of MYL-1501D (process VI), and Lantus-US.

Safety Pharmacology

The Applicant did not perform safety pharmacology studies with MYL-1501D and relies upon the safety pharmacology studies performed in mice, rats, guinea pigs, and dogs supporting approval of Lantus-US.

Pharmacokinetics/ADME/Toxicokinetics

The only comparative pharmacokinetic evaluation of MYL-1501D (Process VI) and Lantus-US was performed as part of a 28-day repeat dose rat toxicity study. Wistar rats were treated subcutaneously with 0, 0.08, 0.16, or 0.38 mg/kg MYL-1501D (Process VI), or Lantus-US, and blood was collected at time 0 (pre-dose), 0.25, 0.5, 1, 2, 3, 4, 6, and 8 hours from 3 rats per group per time point. The pharmacokinetic analysis of MYL-1501D (Process VI) and Lantus-US showed similar pharmacokinetic parameters.

Pharmacokinetics Drug Interactions

Applicant did not perform any nonclinical drug-drug interactions studies, but instead relies on the information described in Lantus-US labeling, which includes medications that may potentiate as well as medications that may reduce the blood glucose-lowering effect of Lantus-US.

Genetic Toxicology

Applicant has not performed any Genetic Toxicology study with MYL-1501D and relies on the Genetic Toxicology information referenced in Lantus-US label.

Carcinogenicity

Applicant has not performed any Carcinogenicity study with MYL-1501D and relies on the Carcinogenicity information referenced in Lantus-US label.

Reproductive and Developmental Toxicology

Applicant has not performed any Reproductive and Developmental Toxicology studies with MYL-1501D and relies on the Reproductive and Developmental Toxicology information referenced in Lantus-US label.

From the nonclinical perspective, the comparability of MYL-1501D (Process VI) and Lantus-US was established by the Applicant by performing comparative in vitro and in vivo pharmacology and toxicology studies and on relying in part, on prior approval of the U.S. listed drug Lantus (insulin glargine for injection – NDA 021081).

12 Appendix

Reviewer's Recommended Labeling

1 INDICATIONS AND USAGE

SEMGLEE is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

Limitations of Use

SEMGLEE is not recommended for the treatment of diabetic ketoacidosis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: (b) (4)

(b) (4)

Data

Human Data: (b) (4)

(b) (4)

Animal Data: Subcutaneous reproduction and teratology studies have been performed with (b) (4) *insulin glargine* (b) (4) *and* (b) (4) *regular human insulin in rats and*

Himalayan rabbits. [redacted] insulin glargine [redacted] was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately [redacted] times the recommended human subcutaneous starting dose of [redacted] mg/kg/day), based on mg/m^2. In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of [redacted] mg/kg/day), [redacted]. The effects of [redacted] insulin glargine [redacted] did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In mice and rats, standard two-year carcinogenicity studies with another insulin glargine product were performed at doses up to 0.455 mg/kg, which was for the rat approximately [redacted] times [redacted] the recommended human subcutaneous starting dose of [redacted] mg/kg/day), [redacted] Histiocytomas were found at injection sites in male rats [redacted] and [redacted] mice [redacted] in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. [redacted]

Another insulin glargine product was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames-and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

In a combined fertility and prenatal and postnatal study of another insulin glargine product in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which was approximately [redacted] times the recommended human subcutaneous starting dose of [redacted] mg/kg/day), [redacted], maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH insulin.

Applicant's proposed PLLR-compliant labeling

DRAFT PRESCRIPTION LABEL FOR SEMGLEE

DRAFT LABELING

3 Pages of Draft Labeling have been Withheld in Full as B4(CCI/ TS) Immediately Following this Page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARULASANAM K THILAGAR
04/10/2018

CALVIN L ELMORE
04/10/2018
I concur.