# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761201Orig1s000

# MULTI-DISCIPLINE REVIEW

**Summary Review**
**Office Director**
**Cross Discipline Team Leader Review**
**Clinical Review**
**Non-Clinical Review**
**Statistical Review**
**Clinical Pharmacology Review**

# BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

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| **Application Type** | 351(k) BLA |
| **Application Number** | BLA 761201 |
| **Received Date** | July 29, 2020 |
| **BsUFA Goal Date** | July 29, 2021 |
| **Division/Office** | Division of Diabetes, Lipid Disorders, and Obesity / Office of Cardiology, Hematology, Endocrinology, and Nephrology |
| **Review Completion Date** | See DARRTS stamped date |
| **Product Code Name** | MYL-1501D |
| **Proposed Nonproprietary Name[1]** | insulin glargine-yfgn |
| **Proposed Proprietary Name[1]** | Semglee |
| **Pharmacologic Class** | Long-acting human insulin analog |
| **Applicant** | Mylan Pharmaceuticals Inc. |
| **Applicant Proposed Indication(s)** | To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.<br>Limitations of use: Semglee is not recommended for the treatment of diabetic ketoacidosis |
| **Recommendation on Regulatory Action** | Approval as interchangeable biosimilar to U.S.-Lantus (insulin glargine) |

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
DMPP = Division of Medical Policy Programs
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPV = Division of Pharmacovigilance
DPMH = Division of Pediatric and Maternal Health
CDRH = Center for Devices and Radiological Health
ADL = Associate Director of Labeling

## Glossary

| | |
|---|---|
| AC | Advisory Committee |
| ADA | Anti-drug Antibodies |
| AE | Adverse Event |
| ANCOVA | Analysis of covariance |
| Anti-HCP | Anti-host cell protein |
| BL | Baseline |
| BLA | Biologics License Application |
| BMER | Biosimilar Multidisciplinary Evaluation and Review |
| BMI | Body Mass Index |
| BPCI Act | Biologics Price Competition and Innovation Act |
| BPD | Biosimilar Biological Product Development |
| BsUFA | Biosimilar User Fee Agreements |
| CAA | Comparative Analytical Assessment |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CMC | Chemistry, Manufacturing, and Controls |
| CRF | Case Report Form |
| CRL | Complete Response Letter |
| CRO | Contract Research Organization |
| CRP | C-reactive Protein |
| CSC | Computational Science Center |
| CTD | Common Technical Document |
| CV | Coefficient of Variation |
| DDLO | Division of Diabetes, Lipid Disorders, and Obesity |
| DEPI | Division of Epidemiology |
| DIA | Division of Inspectional Assessment |
| DMC | Data Monitoring Committee |
| DMA | Division of Microbiology Assessment |
| DMEPA | Division of Medication Error Prevention and Analysis |
| DPMH | Division of Pediatric and Maternal Health |
| DRISK | Division of Risk Management |
| ECG | Electrocardiogram |
| eCTD | Electronic Common Technical Document |
| EU-Lantus | European Union-approved Lantus |
| FCA | Further Consolidated Appropriations |
| FDA | Food and Drug Administration |
| FDCA | Federal Food, Drug, and Cosmetic Act |
| FISH | Fluorescence In Situ Hybridization |
| FPG | Fasting plasma glucose |

| | |
|---|---|
| GCP | Good Clinical Practice |
| GMR | Geometric Mean Ratio |
| HbA1c | Hemoglobin A1c (Glycosylated Hemoglobin) |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IFU | Instructions for Use |
| IGF-1 | Insulin Growth Factor-1 |
| IND | Investigational New Drug |
| IP | Investigational Product |
| IR | Insulin receptor |
| IRB | Institutional Review Board |
| ITT | Intention to Treat |
| KG | Kilogram |
| LLOQ | Lower Limit of Quantitation |
| LS | Least Squares |
| MAPP | Manual of Policy and Procedure |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified Intention to Treat |
| MMRM | Mixed-effects model approach |
| MOA | Mechanism of Action |
| NAb | Neutralizing Antibody |
| NCI-CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| NCT | National Clinical Trial |
| NDA | New Drug Application |
| OBP | Office of Biotechnology Products |
| OCP | Office of Clinical Pharmacology |
| OPDP | Office of Prescription Drug Promotion |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigations |
| OSIS | Office of Study Integrity and Surveillance |
| PD | Pharmacodynamics |
| PeRC | Pediatric Review Committee |
| PFP | Pre-filled pen |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PMC | Postmarketing Commitments |
| PMR | Postmarketing Requirements |
| PREA | Pediatric Research Equity Act |
| PHS | Public Health Service |
| PLR | Physician Labeling Rule |
| PLLR | Pregnancy and Lactation Labeling Rule |
| PP | Per Protocol |
| PT | Preferred Term |
| REML | Restricted maximum likelihood |

| | |
|---|---|
| REMS | Risk Evaluation and Mitigation Strategies |
| ROA | Route of Administration |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SD | Standard Deviation |
| SE | Standard Error |
| SGE | Special Government Employee |
| SMBG | Self-monitored blood glucose |
| SOC | System Organ Class |
| SOP | Standard Operating Procedures |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |
| TDD | Total daily dose |
| TEAE | Treatment-Emergent Adverse Events |
| TEAR | Treatment-Emergent Antibody Response |
| ULOQ | Upper Limit of Quantitation |
| U.S.-Lantus | U.S.-licensed Lantus |
| USPI | U.S. Prescribing Information |
| %SB | Percent specific binding |

# 1. Executive Summary

## 1.1. Product Introduction

Mylan (hereafter referred to as "the Applicant") submitted a biologic license application (BLA) under section 351(k) of the Public Health Service (PHS) Act for MYL-1501D as a proposed intechangeable biosimilar to U.S.-Lantus (insulin glargine). MYL-1501D (proposed non-proprietary name insulin glargine-yfgn; proposed proprietary name SEMGLEE) is a long-acting human insulin analog. The sequence of MYL-1501D (and U.S.-Lantus) is homologous with regular human insulin with the exception of a substitution of the amino acid glycine by asparagine at position A21 and two arginine residues added to the C-terminus of the β-chain. MYL-1501D is produced by recombinant DNA technology utilizing *Pichia pastoris*. MYL-1501D is supplied at 100 units/mL (U-100) in both a 3 mL single patient use, multi-dose pre-filled pen (PFP) and also a 10 mL multiple-dose vial for subcutaneous injection.

The Applicant is seeking licensure of MYL-1501D for the following indication for which U.S.-Lantus has been previously approved:

- to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM).

  Limitations of use: Semglee is not recommended for the treatment of diabetic ketoacidosis

## 1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

The Applicant submitted animal studies to support its 351(k) application. However, given the absence of detectable differences in the results from the battery of *in vitro* assays, and given that the results from the euglycemic clamp study support a demonstration of PK similarity, animal studies would not be informative to the evaluation of toxicity (see section 4.1 for additional information). Moreover, as also described in this review, the applicant's comparative analytical and clinical data supports a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between MYL-1501D and U.S.-licensed Lantus in terms of safety, purity and potency. Accordingly, FDA has determined that the animal studies are unnecessary in this 351(k) application and therefore, the *in vivo* animal toxicology studies were not reviewed.

## 1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

The primary activity of insulin and its analogs, including U.S.-Lantus, is regulation of glucose metabolism through binding and activation of insulin receptors. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

Comparative analytical testing including multiple orthogonal assays relevant to the mechanism of action of U.S.-Lantus, plus comparative clinical pharmacodynamic data evaluating glucose metabolism, demonstrated that MYL-1501D has the same mechanism of action as that of U.S.-Lantus, to the extent known.

MYL-1501D is proposed as below:

ROUTE OF ADMINISTRATION: subcutaneous injection

DOSAGE FORM: injection

STRENGTH: 300 units per 3 mL single-patient use pre-filled pen and 1000 units per 10 mL multiple-dose vial; 100 units/mL.

Each strength of MYL-1501D in the pre-filled pen and the vial is the same as that of U.S.-Lantus. MYL-1501D also has the same dosage form and route of administration as that of U.S.-Lantus.

Additionally, the conditions of use for which the applicant is seeking licensure have been previously approved for U.S.-Lantus.

## 1.4. Inspection of Manufacturing Facilities

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination strategy were provided for Biocon Sdn. Bhd. (FEI 3011248248), proposed for DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage. OBP and OPMA concurred that an on-site inspection of this facility (Biocon Sdn. Bhd.) was not necessary.

## 1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

Not Applicable. Data generated from studies using E.U.-approved Lantus were not used to support a demonstration of biosimilarity or interchangeability.

## 1.6. Biosimilarity and Interchangeability Assessment

**Table 1: Summary and Assessment of Biosimilarity and Interchangeability**

| **Comparative Analytical Studies[2]** | |
|---|---|
| Summary of Evidence | • MYL-1501D is highly similar to U.S.-licensed Lantus, notwithstanding minor differences in clinically inactive components. MYL-1501D has the same strength, dosage form, and route of administration as those of U.S.-licensed Lantus. The Applicant used a comprehensive array of analytical methods that were suitable to evaluate critical quality attributes of MYL-1501D and U.S.-licensed Lantus to support the demonstration that the products are highly similar. While differences were observed in a limited number of attributes, these do not preclude a demonstration that MYL-1501D is highly similar to U.S.-licensed Lantus. |
| Assessment of Residual Uncertainties | • There are no residual uncertainties from the product quality assessement |
| **Nonclinical Studies** | |
| Summary of Evidence | • *In vitro* studies evaluating the insulin receptor (IR) and insulin-like growth factor-1 (IGF-1) receptor binding, IR activation, metabolic activity, and mitogenic activity (IR- and IGF-1 receptor-dependent) of MYL-1501D and U.S.-Lantus demonstrated MYL-1501D to be similar to U.S.-Lantus.<br>• *In vitro* studies support the demonstration of biosimilarity.<br>• FDA has determined that the animal studies are unnecessary in this 351(k) application and therefore the *in vivo* animal toxicology studies were not reviewed. |
| Assessment of Residual Uncertainties | • There are no residual uncertainties from the pharmacology/toxicology perspective. |

[2]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

| **Clinical Studies** | |
|---|---|
| ***Clinical Pharmacology Studies*** | |
| Summary of Evidence | • PK and PD similarity between MYL-1501D and US-Lantus were demonstrated in healthy subjects using the pre-filled pen formulation (Study MYL-1501D-1003).[3]<br>• PK comparability between MYL-1501D vial formulation and MYL-1501D prefilled pen formulation were demonstrated in healthy subjects (Study MYL-1501D-1004). PD comparability was evaluated and also demonstrated.<br>• PK and PD data from Studies MYL-1501D-1003 and MYL-1501D-1004 add to the totality of evidence to support a demonstration of no clinical meaningful differences between MYL-1501D and U.S.- Lantus. |
| Assessment of Residual Uncertainties | • There are no residual uncertainties from a clinical pharmacology perspective. |
| ***Additional Clinical Studies*** | |

[3] The formulation composition of MYL-1501D and U.S.-Lantus are the same (i.e., the excipients in MYL-1501D prefilled pen and vial presentations are the same and present in the same levels as the excipients in U.S.-Lantus in the pre-filled pen and vial presentations, respectively). See Section 4.2 for more information.

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| Summary of Evidence | • FDA determined that, based on the information in the application, including the applicant's immunogenicity assessment, a clinical immunogenicity study comparing MYL-1501D and U.S.-Lantus is not necessary in this 351(k) application<br>• The Applicant submitted clinical studies that evaluated the safety, efficacy, and immunogenicity of MYL-1501D compared to that of U.S.-Lantus. Most of the studies submitted had been previously reviewed under NDA 210605.[4] No clinical data comparing MYL-1501D to U.S.-Lantus, other than the euglycemic clamp PK/PD studies MYL-1501D-1003 and MYL-1501D-1004, were necessary to support a demonstration of biosimilarity of MYL-1501D and U.S.-Lantus. The additional clinical data provided by the applicant that were not necessary to support the demonstration of biosimilarity did not preclude or conflict with conclusions based on other data and information. |
| Assessment of Residual Uncertainties | • There are no residual uncertainties from the clinical perspective. |
| ***Switching Study*** | |

[4] NDA 210605 was approved on June 11, 2020. Upon approval, the marketing application ceased to exist as a new drug application and was deemed to be an approved BLA under section 351(a) of the PHS Act.

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| Summary of Evidence | • The Applicant provided adequate data and information, including an adequate immunogenicity assessment, to justify why a clinical immunogenicity study comparing MYL-1501D and U.S.-Lantus was not necessary to support the demonstration that the risk in terms of safety or diminished efficacy of alternating or switching between use of MYL-1501D and U.S.-Lantus is not greater than the use of U.S.-Lantus without such switch or alternation.<br>• In addition, the Applicant submitted clinical data not previously reviewed from a "switching study" (Study MYL-1501D-3003) that was conducted without agreement with FDA on its design. Although the data submitted were unnecessary to support a demonstration of interchangeability of MYL-1501D and U.S.-Lantus, the data provided did not preclude or conflict with conclusions based on other data and information. |
| | • There are no residual uncertainties from the clinical perspective. |
| **Any Given Patient Evaluation** | |
| Summary of Evidence | • The data submitted in the application, including the comparative analytical data and comparative pharmacodynamic and pharmacokinetic data, support a demonstration that MYL-1501D can be expected to produce the same clinical result as that of U.S.-Lantus in any given patient. The Applicant has provided adequate data and information to support a demonstration that MYL-1501D can be expected to produce the same clinical result as U.S.-Lantus in any given patient. |
| Assessment of Residual Uncertainties | • There are no residual uncertainties from the clinical perspective. |
| **Extrapolation** | |

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| Summary of Evidence | • The information submitted in the application, including the comparative analytical data and the PK/PD results (which together demonstrate that the mechanism of action is the same in MYL-1501D and U.S.-Lantus, to the extent known) supports a demonstration that MYL-1501D and U.S.-Lantus are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of safety, purity, and potency. The information in the BLA also supports a demonstration that MYL-1501D can be expected to produce the same clinical result as U.S.-Lantus in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of MYL-1501D and U.S.-Lantus is not greater than the use of U.S.-Lantus without such switch or alternation. An extrapolation of the finding of PK similarity of MYL-1501D and U.S.-Lantus in healthy adults to adult patients with T1DM, pediatric patients with T1DM, and adult patients with T2DM is justified because the same scientific factors that determine absorption, distribution, metabolism, and elimination in healthy adults also determine absorption, distribution, metabolism, and elimination in patients with diabetes mellitus. The extrapolation of the finding of PD similarity of MYL-1501D and U.S.-Lantus in healthy adults to adult patients with T1DM, pediatric patients with T1DM and adult patients with T2DM is justified because the assessed PD endpoints evince the binding and activation of insulin receptors, which is the pertinent MOA for all conditions of use of U.S. Lantus (to the extent known). No comparison of any other scientific factors across the conditions of use were necessary to justify the extrapolation. The extrapolation does not require specific knowledge about the relationship between the PK and PD profiles observed in healthy adults and the PK and PD profiles that would be observed in patients with diabetes mellitus.<br>• The data and information in the application, including comparative pharmacokinetic and |

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|---|---|
| | pharmacodynamic data demonstrating no meaningful differences in time-concentration profile and time-action profile over the duration of action of each product, from Studies 1003 and 1004, supports licensure for the conditions of use for which U.S.-Lantus has been previously approved and for which the applicant is seeking licensure.<br>• The information submitted by the applicant demonstrates that MYL-1501D is biosimilar to and interchangeable with U.S.-Lantus for the following indication (including all of the indicated patient populations) for which the Applicant is seeking licensure and for which U.S.-Lantus has been previously approved: to improve glycemic control in adults and pediatric patients with T1DM and in adults with T2DM. |
| Assessment of Residual Uncertainties | • There are no residual uncertainties. |

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of the Affordable Care Act, which President Obama signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the "reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific nonclinical and clinical data.

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a "stand-alone" marketing application). The goal of a "stand-alone" development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

As detailed in *Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products* (November 2019) *('Insulin Immunogenicity Guidance')*, FDA has determined that applicants for biosimilar and interchangeable

insulin products may provide an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimiliarity for an insulin product. Further, for proposed interchangeable insulin products demonstrated to be “highly similar” to the reference product with very low residual uncertainty about immunogenicity, FDA has determined that applicants would generally not need to conduct a comparative clinical immunogenicity study, e.g., a switching study, to support licensure under 351(k)(4) of the PHS Act so long as the statutory criteria for licensure as an interchangeable are otherwise met.

On review of BLA 761201, including the immunogenicity assessment, FDA determined that a clinical immunogenicity study comparing MYL-1501D and U.S.-Lantus was not necessary to support a demonstration of biosimilarity or interchangeability of MYL-1501D and U.S. Lantus. Consistent with the *Insulin Immunogenicity Guidance*, the data submitted by the Applicant, including a comprehensive and robust comparative analytical assessment and comprehensive clinical pharmacology studies that provide time-concentration profile and time-action profile over the duration of MYL-1501D and U.S.-Lantus based on reliable measures of systemic exposure and glucose response using a euglycemic clamp procedure, support a demonstration that MYL-1501D is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between MYL-1501D and U.S.-Lantus in terms of safety, purity, and potency. The information in the BLA also supports a demonstration that MYL-1501D can be expected to produce the same clinical result as the U.S.-Lantus in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of MYL-1501D and U.S.-Lantus is not greater than the use of U.S.-Lantus without such switch or alternation.

The information submitted in the application, including the comparative analytical data and the PK/PD results (which together demonstrate that the mechanism of action is the same in MYL-1501D and U.S.-Lantus, to the extent known) supports a demonstration that MYL-1501D and U.S.-Lantus are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of safety, purity, and potency. The information in the BLA also supports a demonstration that MYL-1501D can be expected to produce the same clinical result as U.S.-Lantus in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of MYL-1501D and U.S.-Lantus is not greater than the use of U.S.-Lantus without such switch or alternation. An extrapolation of the finding of PK similarity of MYL-1501D and U.S.-Lantus in healthy adults to adult patients with T1DM, pediatric patients with T1DM, and adult patients with T2DM is justified because the same scientific factors that determine absorption, distribution, metabolism, and elimination in healthy adults also determine absorption, distribution, metabolism, and elimination in patients with diabetes mellitus. The extrapolation of the finding of PD similarity of MYL-1501D and U.S.-Lantus in healthy adults to adult patients with T1DM, pediatric patients with T1DM and adult patients with T2DM is justified because the assessed PD endpoints evince the binding and activation of insulin

receptors, which is the pertinent MOA for all conditions of use of U.S. Lantus (to the extent known). No comparison of any other scientific factors across the conditions of use were necessary to justify the extrapolation. The extrapolation does not require specific knowledge about the relationship between the PK and PD profiles observed in healthy adults and the PK and PD profiles that would be observed in patients with diabetes mellitus. The data and information in the application, including comparative pharmacokinetic and pharmacodynamic data demonstrating no meaningful differences in time-concentration profile and time-action profile over the duration of action of each product, from Studies 1003 and 1004, supports licensure for the conditions of use for which U.S.-Lantus has been previously approved and for which the applicant is seeking licensure.

The analytical data submitted in BLA 761201 included material manufactured using both MYL-1501D Process V and MYL-1501D Process VI. Comparability between lots manufactured using Process V and VI was established based on analytical data, study MYL-1501D-1003, and study MYL-1501D-3004; the data from MYL-1501D-3004 was only needed to demonstrate comparability and was not otherwise relied upon to demonstrate biosimilarity or interchangeability (see section 2.2). Therefore, once comparability had been established, on review of BLA 761201 and consistent with the Insulin Immunogenicity Guidance, FDA determined that no additional clinical data other than the data from the comparative clinical studies MYL-1501D-1003 and MYL-1501D-1004 were necessary to support a demonstration that MYL-1501D is biosimilar to an interchangeable with U.S.-Lantus.

See the discussion in **Section** Error! Reference source not found. for details regarding the review of the immunogenicity assessment of MYL-1501D.

## 1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that MYL-1501D is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between MYL-1501D and U.S.-Lantus in terms of the safety, purity, and potency of the product. The information submitted by the Applicant demonstrates that MYL-1501D is biosimilar to U.S.-Lantus for the following indication for which U.S.-Lantus has been previously approved and for which the Applicant is seeking licensure of MYL-1501D: to improve glycemic control in adults and and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

The data and information provided by the Applicant are sufficient to demonstrate that MYL-1501D can be expected to produce the same clinical result as U.S.-licensed Lantus in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of MYL-1501D and U.S.-Lantus is not greater than the risk of using U.S.-Lantus without alternation or switch.

The Applicant also provided adequate data and information, including an adequate

immunogenicity assessment, to justify that a comparative clinical immunogenicity study is not necessary to support a demonstration of biosimilarity and interchangeability to U.S.-Lantus.

Therefore, the information submitted by the Applicant demonstrates that MYL-1501D is biosimilar to and interchangeable with U.S.-licensed Lantus for the following indication, for which U.S.-licensed Lantus has been previously approved and for which the Applicant is seeking licensure: to improve glycemic control in adults and and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

There are no biological products relying on the reference product for MYL-1501D 10 mL vial or MYL-1501D 3 mL prefilled pen that have received a determination of interchangeability for any condition of use. MYL-1501D 10 mL vial and MYL-1501D 3 mL prefilled pen are the first biological products relying on their respective reference products to receive a determination of interchangeability for any condition of use.

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Associate Director for Therapeutics, DDLO

# 2. Introduction and Regulatory Background

## 2.1. Summary of Presubmission Regulatory History Related to Submission

The following section summarizes the regulatory history of MYL-1501D under IND 140431 prior to the submission of its 351(k) biologics license application (BLA).

In July 2018, the Applicant opened pre-IND (investigational new drug) 140431 in order to join the Biosimilar Biological Product Development (BPD) Program and discuss the development of MYL-1501D. Below is a summary of the key regulatory interactions between FDA and the Applicant under pre-IND 140431 prior to the Applicant's submission of the current 351(k) application.

- October 2018: BPD Type 2 Meeting
    - The Applicant presented the design of the MYL-1501D-3003 study and inquired if it could address the statutory provision set forth in Section 351(k)(4)(B) of the PHS Act, which defines the safety standards for determining interchangeability.
    - FDA did not agree with the Applicant's choice of glycosylated hemoglobin (HbA1c) as the primary endpoint. Both parties agreed that HbA1c was too insensitive of an endpoint to serve as the only basis on which to conclude that the risk of switching between MYL-1501D and U.S.-licensed Lantus in

terms of safety or diminished efficacy was not greater than using U.S.-licensed Lantus without switching. Both parties also agreed that use of PK endpoints alone may not be feasible to detect differences between MYL-1501D and U.S.-licensed Lantus. FDA also stated that a switching study should assess differences in immunogenicity.
    - FDA noted that the threshold analysis submitted under pre-IND 140431 was not conducted with the intended-to-market instructions for use (IFU). FDA requested the Applicant submit a new threshold analysis including the intended-to-market IFU for the proposed product for which they were seeking interchangeability.

- November 25, 2019: FDA issued Advice Letter to the Applicant
    - This letter informed the Applicant of FDA's updated scientific thinking on issues that had been discussed at the October 2018 BPD Type 2 meeting. FDA referenced the draft guidance for industry, *Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products* (November 2019)[5] (hereafter referred to as the "*Insulin Immunogenicity Guidance*").
    - Consistent with this draft guidance, FDA explained the updated thinking that a comparative clinical immunogenicity study generally would be considered unnecessary to support a demonstration of biosimilarity or interchangeability for the Applicant's proposed insulin product if the comparative analytical assessment adequately supported a demonstration of highly similar as part of a demonstration of biosimilarity.
    - FDA still expected a clinical pharmacology study or studies, such as a comparative PK/PD study.
    - FDA also noted that a comparative clinical immunogenicity study may still be necessary as a scientific matter to support licensure, for example, if there were differences in certain impurities or novel excipients that gave rise to questions or residual uncertainty related to immunogenicity of the Applicant's proposed insulin product.
    - FDA stated that if the Applicant intended to pursue licensure of MYL-1501D as a biosimilar to U.S.-Lantus under Section 351(k) of the PHS Act and the Applicant believed that data from a comparative clinical immunogenicity study may not be necessary, FDA recommended that the submission include an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity for their proposed product.
    - In addition, FDA noted that its scientific thinking is that if the Applicant is able to demonstrate biosimilarity between MYL-1501D and U.S.-Lantus without conducting a comparative clinical immunogenicity study, then generally such a study would not be needed as part of a demonstration that MYL-1501D is interchangeable with U.S.-Lantus.

[5] Food and Drug Administration. Draft guidance for industry: Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products, November 2019, accessed from: https://www.fda.gov/media/133014/download

- July 2020: BPD Type 2 meeting Written Responses
    - FDA reiterated to the Applicant the regulatory pathway and data needed to support a demonstration that MYL-1501D is interchangeable with U.S.-Lantus. FDA advised the Applicant to refer to the Advice letter issued on November 25, 2019 and the Insulin Immunogenicity Guidance
    - FDA noted that the applicant is seeking licensure for the same indication (including populations) as U.S.-licensed Lantus, and that for the pediatric populations for which U.S.-licensed Lantus is not approved, there are no pending PREA postmarketing requirements. A pediatric assessment for MYL-1501D would not be expected to include pediatric studies with MYL-1501D and a waiver need not be requested.

## 2.2. Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

**Table 2. Nonclinical Studies**

| Study Title | Study Number | Study Type | Test System | Test Article(s) |
|---|---|---|---|---|
| Sample Analysis for Assessing the Binding Kinetics of Insulin Glargine to Insulin Receptor (Short form) Using Biacore | U-15325 | Insulin Receptor-A Binding Kinetics | Biochemical acellular purified protein | MYL-1501D, US-Lantus, and EU-Lantus |
| Sample Analysis for Assessing the Binding Kinetics of Insulin Glargine to Insulin Receptor (Short form) Using Biacore | U-16335 | Insulin Receptor-A Binding Kinetics | Biochemical acellular purified protein | MYL-1501D, US-Lantus, and EU-Lantus |
| Sample Analysis for Assessing the Binding Kinetics of Insulin Glargine to Insulin Receptor (Long form) Using Biacore | U-16336 | Insulin Receptor-B Binding Kinetics | Biochemical acellular purified protein | MYL-1501D, US-Lantus, and EU-Lantus |
| Sample Analysis for Assessing the Binding Kinetics of Insulin Glargine to Insulin Receptor | U-15309 | Insulin Receptor-B Binding Kinetics | Biochemical acellular purified protein | MYL-1501D, US-Lantus, and EU-Lantus |

| Study Title | Study Number | Study Type | Test System | Test Article(s) |
|---|---|---|---|---|
| (Long form) Using Biacore | | | | |
| Side by Side Comparability Assessment of Biocon's Insulin Glargine with EU and US Sourced Lantus Reference Product by In-Vitro Bioassays | BDL/TR/ BR.15.0003/16/ 002 | Insulin Like Growth Factor-1 (IGF-1) Receptor Binding Kinetics | Biochemical acellular purified protein | MYL-1501D, US-Lantus, and EU-Lantus |
| Side by Side Comparability Assessment of Biocon's Insulin Glargine with EU and US Sourced Lantus Reference Product by In-Vitro Bioassays | BDL/TR/ BR.15.0003/16/ 002 | Insulin Receptor-A Phosphorylation, Insulin Receptor-B Phosphorylation, and Total Insulin Receptor Phosphorylation | Engineered CHO-K1 cells overexpressing insulin receptor-A and/or insulin receptor-B | MYL-1501D, US-Lantus, and EU-Lantus |
| Side by Side Comparability Assessment of Biocon's Insulin Glargine with EU and US Sourced Lantus Reference Product by In-Vitro Bioassays | BDL/TR/ BR.15.0003/16/ 002 | Glucose Uptake/ Metabolism | Differentiated 3T3-L1 Cells | MYL-1501D, US-Lantus, and EU-Lantus |
| Comparability Studies Evaluating the Adipogenic Potential of Innovator Insulin Glargine Reference Products and Biocon In-house Insulin Glargine Batches in 3T3-L1 Cells | RPT MBN-007 | Adipogenesis/ Metabolism | Differentiated 3T3-L1 Cells | MYL-1501D, US-Lantus, and EU-Lantus |
| Comparability Studies Evaluating the Lipolysis Inhibition Potential of Innovator Insulin Glargine Reference Products and Biocon In-house Insulin Glargine Batches in 3T3-L1 Cells | RPT-MBN-010 | Lipolysis Inhibition/ Metabolism | Differentiated 3T3-L1 Cells | MYL-1501D, US-Lantus, and EU-Lantus |

| Study Title | Study Number | Study Type | Test System | Test Article(s) |
|---|---|---|---|---|
| Side by Side Comparability Assessment of Biocon's Insulin Glargine with EU and US Sourced Lantus Reference Product by In-Vitro Bioassays | BDL/TR/ BR.15.0003/16/ 002 | IGF-1 Receptor-Dependent Mitogenicity Activity | Saos2 cells / human osteosarcoma cell line expressing the IGF-1 receptor | MYL-1501D, US-Lantus, and EU-Lantus |
| Assessment of Insulin Glargine MYL-1501D and US licensed Lantus Drug Product Batches by Mitogenic Assay in H4IIE Cell Line | BDL/TR/LR.19.0 091/21/002 | Insulin Receptor-Dependent Mitogenicity Activity | H4IIE cells / rat hepatoma cells overexpressing insulin receptor-A | MYL-1501D and US-Lantus |

## Table 3. Listing of All Submitted Clinical Studies

| Study Identity | National Clinical Trial (NCT) no. | Study Objective | Study Design | Study Population | Treatment Groups |
|---|---|---|---|---|---|
| **PK/PD Similarity Studies** | | | | | |
| Study GLARGC T100111 | Clinical trial registration: EudraCT, 2011-003563-30 | To compare the relative PK and PD properties of MYL-1501D Process V, US-Lantus, and EU-Lantus | Single-center, randomized, double blind, single-dose, 3-way crossover euglycemic clamp; active control (US-Lantus and EU-Lantus) | T1DM patients | 114 randomized<br>112 completed all three treatments<br><br>MYL-1501D Process V: 112<br>US-Lantus: 112<br>EU-Lantus: 114 |
| Study MYL-1501D-1001 | | To compare the PK and PD of MYL-1501D Process V, MYL-1501D Process VI, and US-Lantus | Randomized, double-blind, single dose, 3-treatment, 3-period crossover, euglycemic glucose clamp; active control US-Lantus | T1DM patients | 116 randomized<br><br>113 completed all 3 treatments<br>MYL-1501D Process V: 113<br>MYL-1501D Process VI: 115<br>US-Lantus: 113 |
| Study MYL-1501D-1003 | | To compare PK and PD parameters and safety between MYL-1501D Process V, MYL-1501D Process VI, and US-Lantus | Randomized, double-blind, single-dose, three-treatment, six period, six sequence, fully replicated, euglycemic glucose clamp study in healthy | Healthy subjects | 95 Randomized<br><br>74 completed the study |

| Study Identity | National Clinical Trial (NCT) no. | Study Objective | Study Design | Study Population | Treatment Groups |
|---|---|---|---|---|---|
| | | | subjects<br>Used cartridges (i.e., prefilled pen formulation) | | |
| Study MYL-1501D-1004 | | To demonstrate PK and PD comparability of MYL-1501D Process VI formulation in vial vs. cartridge (i.e. prefilled pen formulation) | Randomized, double-blind, single-dose, fully replicated 4-way crossover, 2 treatment euglycemic glucose clamp study | Healthy subjects | 48 randomized<br><br>45 completed the study |
| **Comparative Clinical Study(ies)** | | | | | |
| Study MYL-GAI-3001 | NCT02227862 | To test for non-inferiority in change in HbA1c (change from baseline to 24 weeks) between MYL-1501D Process V and US-Lantus | Open-label, randomized, multicenter, parallel assignment, active control (US-Lantus). Used prefilled pen presentation | T1DM patients | 558 randomized<br>MYL-1501D Process V: 280<br>US-Lantus: 278<br><br>517 completed<br>MYL-1501D Process V: 261<br>US-Lantus: 256 |
| Study MYL-GAI-3002 | NCT02227875 | To test for non-inferiority in change in HbA1C (change from baseline to 24 weeks) between MYL-1501D Process V and US-Lantus | Open-label, randomized, multicenter, parallel assignment; active control (US-Lantus) | T2DM patients | 560 randomized<br>MYL-1501D Process V: 277<br>US-Lantus: 283<br><br>490 completed<br>MYL-1501D Process V: 240<br>US-Lantus: 250 |
| Study MYL-1501D-3003 | NCT02666430 | To compare change in HbA1c when MYL-1501D Process V and US-Lantus are alternated compared to continued treatment with US-Lantus. | Open-label, randomized, multicenter, parallel assignment; active control (US-Lantus) | T1DM patients | 127 randomized<br>MYL-1501D Process V: 64<br>US-Lantus: 63<br><br>119 completed<br>MYL-1501D Process V: 61<br>US-Lantus: 58 |
| Study MYL-1501D-3004 | NCT03376789 | To compare safety and efficacy of MYL-1501D Process VI and MYL-1501D Process V at week 18, when administered in combination with | Randomized, multicenter, double-blinded parallel assignment | T1DM patients | 219 randomized<br>MYL-1501D Process V: 108<br>MYL-1501D Process VI: 111<br><br>205 completed<br>MYL-1501D Process V: 103 |

| Study Identity | National Clinical Trial (NCT) no. | Study Objective | Study Design | Study Population | Treatment Groups |
|---|---|---|---|---|---|
| | | mealtime insulin lispro | | | MYL-1501D Process VI: 102 |

The Applicant submitted the clinical studies listed in Table 3 above to the 351(k) BLA. All of the clinical studies, except for Study MYL-1501D-3003, were also submitted to NDA 210605 and reviewed by FDA under that NDA.[6] The Applicant also submitted analytical data (in addition to clinical data), which was previously submitted to NDA 210605 and reviewed by FDA under that NDA that supported the demonstration of comparability between MYL-1501D Process V and Process VI, to the 351(k) BLA.

Some of these studies used MYL-1501D manufactured using a process identified as "Process V" while others used MYL-1501D manufactured using a process identified as "Process VI." The proposed commercial process for MYL-1501D is identified as "Process VI." Comparability between lots manufactured using Process V and VI has been established based on analytical data, study MYL-1501D-1003, and study MYL-1501D-3004.[7]

Study MYL-1501D-1001 compared the PK and PD profiles of MYL-1501D Process V, MYL-1501D Process VI, and U.S.-Lantus after a single subcutaneous dose of 0.5 unit/kg in a euglycemic clamp study. Although the study results were acceptable to establish PK and PD similarity between MYL-1501D Process VI and U.S.-Lantus and comparability between MYL-1501D Process VI and MYL-1501D Process V, the results were unable to establish PD similarity between MYL-1501D Process V and U.S.-Lantus.

Study GLARGCT100111 compared the PK and PD profiles of MYL-1501D Process V, U.S.-Lantus, and EU-Lantus after a single subcutaneous dose of 0.4 unit/kg in a euglycemic clamp study. The GLARGCT100111 study results were acceptable to establish PK and PD similarity between MYL-1501D Process V and U.S.-Lantus and between E.U.-Lantus and U.S.-Lantus. FDA determined that the results of GLARGCT100111 and MYL-1501D-1001 were not necessary to the demonstration of biosimiliarty or interchangeability of MYL-1501D and U.S.-Lantus. The results of the studies, however, do not preclude or conflict with the conclusion that MYL-1501D and U.S.-Lantus are biosimilar and interchangeable based on other data and information.

The two aforementioned PK/PD studies are not described further in this review because FDA is not relying on them to support a demonstration of biosimilarity or interchangeability. To support these determinations, FDA is relying on, among other things, data from PK/PD studies MYL-1501D-1003 and MYL-1501D-1004. These

[6] NDA 210605 was approved on June 11, 2020. Upon approval, the marketing application ceased to exist as a new drug application and was deemed to be an approved BLA under section 351(a) of the PHS Act.
[7] See Integrated Quality Assessment (finalized in Panorama on March 29, 2021, with subsequent addendums on April 16, 2021 and June 24, 2021) (refering to BLA 210605 CDTL Review and Division Summary Memo for Regulatory Action, June 11, 2020; BLA 210605 OPQ Executive Summary, May 22, 2020; BLA 210605 OPQ Executive Summary, April 5, 2018).

studies are described in this review.

Studies MYL-GAI-3001 and MYL-GAI-3002 were multi-center, open-label, randomized, parallel-group trials designed to compare the efficacy and safety of MYL-1501D Process V with U.S.-Lantus. Study MYL-GAI-3001 included patients with type 1 diabetes mellitus (T1DM) and study MYL-GAI-3002 included patients with type 2 diabetes mellitus (T2DM). Dr. Rauschecker concluded that MYL-1501D Process V was non-inferior to U.S.-Lantus for the primary endpoint of mean change in HbA1c from baseline to week 24 in both phase 3 studies. The review also concluded the safety of MYL-1501D Process V was consistent with the observed safety profile of U.S.-Lantus. Dr. Sonia Doi reviewed study MYL-1501D-3004, comparing MYL-1501D Process V to MYL-1501D Process VI.

This review references FDA's conclusions of studies MYL-GAI-3001 and MYL-GAI-3002 but does not describe the studies in further detail because FDA determined that the results of these clinical trials are not necessary to the demonstration of biosimiliarty or interchangeability of MYL-1501D and U.S.-Lantus. The results of these two studies, however, do not preclude or conflict with the conclusion that MYL-1501D is biosimilar to and interchangeable with U.S.-Lantus based on other data and information.

Additionally, this review references FDA's conclusions based on study MYL-1501D-3004 (see text above and accompanying footnote 7). The analytical data submitted in support of BLA 761201 included material manufactured using not only MYL-1501D Process VI but also MYL-1501D Process V. As study MYL-1501D-3004, among other information, supports a demonstration that MYL-1501D Process V is comparable to MYL-1501D Process VI, it thus supports the demonstration that MYL-1501D is biosimilar to and interchangeable with U.S.-Lantus.

The only clinical study the Applicant submitted to this application that had not been reviewed previously by FDA is study MYL-1501D-3003. This study was designed as a switching study to support a demonstration of interchangeability. However, FDA did not consider the study design appropriate for that purpose. As discussed at the October 2018 BPD Type 2 meeting, the Applicant agreed with FDA that HbA1c was too insensitive to serve as the only basis on which to justify that the risk in terms of safety or diminished efficacy of alternating or switching between use of MYL-1501D and U.S.-Lantus was not greater than using U.S.-Lantus without such alternation or switch.

On review of BLA 761201 and consistent with the '*Insulin Immunogenicity Guidance'*, FDA determined that no additional clinical data other than the data from the comparative clinical pharmacology studies MYL-1501D-1003 and MYL-1501D-1004 (and MYL-1501D-3004 for its support of the demonstration of comparability between MYL-1501D Process V and MYL-1501D Process VI[8]) were necessary to support a demonstration that MYL-1501D is biosimilar to and interchangeable with U.S. Lantus. For that reason,

[8] As noted above, study MYL-1501D-3004, along with additional data and information, supported the demonstration of comparability between Process V and Process VI, as the applicant's analytical data included materials manufactured using both Process V and Process VI.

neither MYL-1501D-3003 nor any other switching study is necessary to support a demonstration of interchangeability with U.S.-Lantus. However, Study MYL-1501D-3003 was reviewed to confirm that its results did not preclude or conflict with conclusions based on other sources of data and information. Because Study MYL-1501D-3003 was not necessary in this 351(k) application, it is discussed in an appendix rather than in the body of the Biosimilar Multidisciplinary Evaluation and Review (BMER).

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# 3. Summary of Conclusions of Other Review Disciplines

## 3.1. Office of Pharmaceutical Quality (OPQ)

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761201 for MYL-1501D manufactured by Mylan. Refer to the Integrated Quality Assessment (finalized in Panorama on March 29, 2021, with subsequent addendums on April 16, 2021 and June 24, 2021) and related primary reviews for detailed information.

Some of the analytical and clinical studies submitted to BLA 761201 used MYL-1501D manufactured using a process identified as “Process V” while others used MYL-1501D manufactured using a process identified as “Process VI.” The proposed commercial process for MYL-1501D is identified as “Process VI.” Comparability between lots manufactured using Process V and VI has been established based on analytical data, study MYL-1501D-1003, and study MYL-1501D-3004.[9]

Some of the analytical and clinical studies submitted to BLA 761201 used MYL-1501D pre-filled pen formulation supplied in cartridges. The cartridge is the primary container closure system of the MYL-1501D pre-filled pen. OBP determined that the assembly process of the cartridge into the pen has no impact on the quality attributes of MYL-1501D.

From a product quality perspective, OPQ did not identify any product quality deficiencies that would preclude approval of BLA 761201 for MYL-1501D. OPQ determined that the data submitted in the application, including the comparative analytical assessment

[9] See Integrated Quality Assessment (IQA) (finalized in Panorama on March 29, 2021, with subsequent addendums on April 16, 2021 and June 24, 2021) (refering to BLA 210605 CDTL Review and Division Summary Memo for Regulatory Action, June 11, 2020; BLA 210605 OPQ Executive Summary, May 22, 2020; BLA 210605 OPQ Executive Summary, April 5, 2018).

between MYL-1501D and U.S.-Lantus, are adequate to support the conclusion that:

- The manufacture of the proposed product is well-controlled and leads to a product that is safe, pure, and potent
- MYL-1501D is highly similar to U.S.-licensed Lantus, nothwithstanding minor differences in clinically inactive components

The proposed presentations of MYL-1501D (10 mL vial and 3 mL pre-filled pen) have the same total content of drug substance in units of mass per unit volume (100 units/mL) as the corresponding presentations of U.S.-licensed Lantus. The strength of MYL-1501D vials and pre-filled pens is the same as those of U.S.-licensed Lantus.

Data generated from studies using E.U.-approved Lantus were not used to support a demonstration of biosimilarity or interchangeability. Therefore analytic testing results from E.U.-approved Lantus were not assessed, as there was no need to establish a scientific bridge.

## 3.2. Devices

### 3.2.1. Center for Devices and Radiological Health (CDRH)

CDRH's Division of Drug Delivery, General Hospital, and Human Factors (DHT3C) reviewed the device component of the pre-filled pen. The combination pre-filled pen product uses the (b) (4) Disposable Pen Device platform, which is the same device platform used for U.S.-Semglee licensed under BLA 210605. The (b) (4) Disposable Pen Device platform has been commercially available to pharmaceutical companies for use with their drug products (b) (4). The combination pre-filled pen product more specifically uses an enhanced model – (b) (4) Disposable Pen (II) – which has been commercially available (b) (4)

he relevant right of reference letters were included in the BLA.

CDRH performed a device review which included an evaluation of the essential performance requirements of both PFPs. Both devices were found to comply with the same dose accuracy performance standard. The injection force was compared as differences between the pens could impact their usability. CDRH reviewed the Applicant's raw data comparing the injection force required for the MYL-1501D PFP injector to the U.S.-Lantus Solostar and, although the data indicated a slightly higher average injection force for U.S.-Lantus Solostar than the Applicant's PFP, the difference was considered to be minor.

DHT3C determined that the device constituent of the combination product is approvable for the proposed indication. Certain device development data is cross-referenced to BLA 210605. BLA 210605 was previously reviewed by CDRH under ICCR2017-01604/ICC1700398.

### 3.2.2. Division of Medication Error Prevention and Analysis (DMEPA)

In a July 3, 2020 written response to a May 8, 2020 BPD type 2 meeting request, the Applicant was advised to submit a comparative task analysis, labeling comparison, and physical comparison between their proposed interchangeable biosimilar product, MYL-1501D, and U.S.-licensed Lantus SoloStar. To support a demonstration of interchangeability, Mylan submitted a physical comparison, comparative task analysis, and labeling comparison of the MYL-1501D pre-filled pen to U.S.-licensed Lantus SoloStar, to identify any differences which may affect the safe and effective use of their product as interchangeable with U.S.-licensed Lantus.

DMEPA reviewed the comparative threshold analyis for MYL-1501D to determine whether the Applicant needed to submit the results of a comparative use human factors study to support their 351(k) application seeking licensure of the MYL-1501D pre-filled pen as an interchangeable biosimilar with U.S.-licensed Lantus. The Applicant submitted a physical comparison, comparative task analysis, and labeling comparison of the proposed MYL-1501D pre-filled pen injector device to U.S.-licensed Lantus SoloStar. DMEPA identified only minor design differences between the proposed MYL-1501D pre-filled pen injector device and U.S.-licensed Lantus SoloStar that do not impact the performance of critical tasks in a meaningful way. DMEPA therefore concluded that the Applicant did not need to submit data from a comparative use human factors study to support the 351(k) application of MYL-1501D as a proposed interchangeable biosimilar with U.S. licensed Lantus.

DMEPA reviewed side by side comparisons of the proposed labels and labeling for MYL-1501D and U.S.-Lantus. DMEPA performed a review of the proposed prescribing information (PI), IFU, container labels, and carton labeling for both the pen and vial presentations to identify areas of vulnerability that may lead to medication errors. DMEPA did not have any concerns with identified differences in container labels and carton labeling (which related to product specific identifiers such as product name). DMEPA determined that the proposed PI and IFU submitted by the Applicant were acceptable from a medication error perspective.

Notwithstanding DMEPA's determination that the proposed PI and IFU submitted by the Applicant were acceptable from a medication error perspective, language and positional differences in comparison to the Lantus PI and IFU were noted. FDA sent the applicant an information request (IR) on June 17, 2021, advising, among other things, that FDA draft Guidance "Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act"[10] recommends that interchangeable biosimilar labeling, like biosimilar labeling, incorporate relevant data and information from the reference product labeling with appropriate modifications. The IR also advised that the recommendations in Section V of the FDA Guidance "Labeling for Biosimilar Products"[11] is generally applicable to interchangeable biosimilars. In the Labeling for Biosimilar

[10] https://www.fda.gov/media/143847/download
[11] https://www.fda.gov/media/96894/download

Products guidance, it recommends that the IFU for the proposed biosimilar product should incorporate relevant information from the IFU for the refence product and present the information in a similar manner. The Applicant subsequently submitted revised labeling. DMEPA had no further comment on the revised PI and IFU.

## 3.3. Office of Study Integrity and Surveillance (OSIS)

MYL-1501D-1003 and MYL-1501D-1004 are, respectively, the clinical pharmacology similarity and comparability studies that comprise the only clinical data relied upon for the demonstration of biosimilarity and interchangeability of MYL-1501D and U.S.-Lantus.

An OSIS audit was not requested for review of BLA 761201. During the review of NDA 210605, the Division of Metabolism and Endocrinology Products issued a request for an OSIS inspection of the clinical and bioanalytical sites of MYL-1501D-1003 and MYL-1501D-1004 on April 10, 2019. The Division of New Drug Bioequivalence Evaluation (DNDBE) within OSIS declined to conduct the inspection. In a memo dated May 3, 2019, DNDBE relayed the following:

- (b) (4): The Office of Regulatory Affairs (ORA) inspected the site in (b) (4) which falls within the surveillance interval. The previously inspected study was conducted within 1 year of MYL-1501D-1004, utilized a similar test product, and involved the same clinical investigator. The final classification for the inspection was No Action Indicated (NAI).
- (b) (4) ORA inspected the site in (b) (4) which falls within the surveillance interval. The previously inspected study was conducted within 1 year of MYL-1501D-1004, utilized a similar test product, and involved the same clinical investigator. The final classification for the inspection was NAI.
- (b) (4) OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: BLA (b) (4) and NDA 210605. The final classification for the inspection was Voluntary Action Indicated (VAI) for observations related to BLA (b) (4) only.

Based on the outcome of the previous inspections, OSIS determined that on-site inspections were not warranted and recommended that all study data be accepted for FDA review.

## 3.4. Office of Scientific Investigations (OSI)

All of the clinical studies listed in Table 3 have been submitted previously to FDA. With the exception of MYL-1501D-3003, all of the clinical studies submitted to BLA 761201 were previously reviewed under NDA 210605. An OSI audit of seven clinical sites and of the Applicant were conducted to support the review of NDA 210605. The inspections revealed no regulatory violations.

Given that study MYL-1501D-3003 was not necessary to support a 351(k) BLA for MYL-1501D, an OSIS audit was not requested for the study.

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# 4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

## 4.1. Nonclinical Executive Summary and Recommendation

Insulins and insulin analogs bind to and activate two isoforms of the insulin receptor formed by alternative splicing of the mRNA: insulin receptor A (IR-A) and insulin receptor B (IR-B). IR-B primarily exerts the metabolic actions of insulin, while IR-A activation serves a developmental function and, owing to its expression in cancer cells, mediates mitogenic and proliferative actions. Mitogenicity of insulin and insulin analogs is also mediated through the insulin-like growth factor-1 (IGF-1) receptor. Comparative analytical data, including in vitro studies evaluating receptor binding, receptor activation, metabolic activity, and mitogenic activity, were submitted to support a demonstration of biosimilarity of MYL-1501D to U.S.-Lantus.

In vitro assays comparing the IR-A and IR-B binding kinetics (association rate [ka]), dissociation rate [kd], and dissociation constant [KD]) of MYL-1501D and U.S.-Lantus, as well as the activation of these receptors (via IR-A and IR-B phosphorylation) in cells overexpressing either IR-B or IR-A demonstrated that the binding kinetics of MYL-1501D to IR-A and IR-B and its ability to activate these insulin receptors were similar to those of U.S.-Lantus. The in vitro binding kinetics of MYL-1501D and U.S.-Lantus at the IGF-1 receptor were also similar. The ability of MYL-1501D and U.S.-Lantus to potentiate mitogenesis was further evaluated in IGF-1 receptor-dependent (Saos2 cells) and IR-dependent (H4IIE cells) mitogenic assays, in which the mitogenic potential of MYL-1501D in the two assays was similar to that of U.S.-Lantus. Lastly, the in vitro metabolic activities of MYL-1501D and U.S.-Lantus as assessed by insulin-stimulated glucose uptake, inhibition of lipolysis, and adipogenesis were similar.

The results of the in vitro studies support a demonstration of biosimilarity between MYL-1501D and U.S.-Lantus.

The E.U.-approved Lantus was included in the in vitro studies as a comparator; however, as data generated with E.U.-approved Lantus was not necessary to support a demonstration of biosimilarity or interchangeability, a scientific bridge to justify the relevance of data generated with E.U.-approved Lantus was not necessary.

From a nonclinical perspective, because the toxicity of insulin glargine products, barring differences in clinical pharmacokinetic (PK) parameters, is a direct function of their affinity and activity at insulin and IGF-1 receptors, the comprehensive battery of in vitro cell-free and cell-based studies are considered more sensitive than animal studies in detecting differences in toxicities, should they exist, between MYL-1501D and U.S.-Lantus, and are thus considered adequate to support an assessment of biosimilarity. The battery of in vitro assays did not detect differences between MYL-1501D and U.S.-Lantus, and PK similarity was evaluated in an euglyemic clamp study in healthy subjects. In the absence of specific pharmacokinetic, physicochemical, or other identifiable concerns, in vivo assays are not anticipated to provide additional meaningful information to inform the evaluation of toxicity.

Accordingly, although two in vivo toxicity studies in rats were submitted, these toxicology studies were not reviewed.

### 4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

## 4.2. Product Information

### Product Formulation

The MYL-1501D drug product is a sterile, clear, and colorless solution at a pH of 4.0 that contains 100 Units/mL of MYL-1501D drug substance. The tables below list the quantitative and qualitative composition of the MYL-1501D drug product in the pre-filled pen and vial presentations. The vials include the additional excipient polysorbate 20, a (b) (4) .

**Qualitative and Quantitative Composition of MYL-1501D Drug Product in the Pre-filled Pen**

| Component | Quantity/mL in MYL-1501D DP | Quality Standard | Function | Quantity/mL in Lantus® presented in cartridges/ pre-filled pen |
|---|---|---|---|---|
| Insulin glargine | 100 Units | In-house | Active ingredient | 100 Units |
| *m*-Cresol | 2.7 mg | Ph. Eur. and USP | (b) (4) | 2.7 mg |
| Glycerol (b) (4) | 20 mg | Ph. Eur. | | 20 mg |
| Zinc (as zinc chloride) | 30 µg | Ph. Eur. and USP | | 30 µg |
| Hydrochloric acid | q.s. | Ph. Eur. and USP | pH adjustment | q.s. |
| Sodium hydroxide | q.s. | Ph. Eur. and USP | pH adjustment | q.s. |
| Water for injection | q.s. to 1 mL | Ph. Eur. and USP | (b) (4) | q.s. to 1 mL |
| DP = Drug Product; Ph. Eur.: European Pharmacopoeia; q.s.: quantity sufficient; USP = United States Pharmacopeia. | | | | |

Source: BLA 761201, Module 3.2.P.2.1, Table 3.2.P.2.1/1

**Qualitative and Quantitative Composition of MYL-1501D Drug Product in the Vial**

| Component | Quantity/mL in MYL-1501D DP presented in vials | Quality standard | Function | Quantity/mL in Lantus presented in vials |
|---|---|---|---|---|
| Insulin glargine | 100 units | In-house | Active ingredient | 100 units |
| *m*-Cresol | 2.7 mg | Ph. Eur. and USP | (b) (4) | 2.7 mg |
| Glycerol (b) (4) | 20 mg | Ph. Eur. | | 20 mg |
| Zinc (as zinc chloride) | 30 µg | Ph. Eur. and USP | | 30 µg |
| Polysorbate 20 | 20 µg | Ph. Eur. and USP | | 20 µg |
| Hydrochloric acid[a] | q.s. | Ph. Eur. and USP | pH adjustment | q.s. |
| Sodium hydroxide[a] | q.s. | Ph. Eur. and USP | pH adjustment | q.s. |
| Water for injection | q.s. to 1 mL | Ph. Eur. and USP | Solvent | q.s. to 1 mL |
| Abbreviations: DP, drug product; Ph. Eur., European Pharmacopoeia; q.s., quantity sufficient; USP, United States Pharmacopeia.<br>[a] Used in the formulation for pH adjustment. | | | | |

Source: BLA 761201, Module 3.2.P.2.1, Table 3.2.P.2.1/1

**Comments on Excipients**

The formulation composition of MYL-1501D and U.S.-Lantus are the same (i.e., the excipients in MYL-1501D prefilled pen and vial formulations are the same and present in the same levels as the excipients in U.S.-Lantus in the pre-filled pen and vial presentations, respectively (refer to the Table below)).

**Formulation Composition of the MYL-1501D Drug Product and U.S.-Lantus (Quantity/mL)**

| Ingredients# | MYL-1501D presented in 3 mL pre-filled pen (Formulation D) | MYL-1501D presented in 10 mL vials (Formulation D with polysorbate 20) | Quantity/mL in Lantus presented in 3 mL cartridges/pre-filled pen | Quantity/mL in Lantus presented in 10 mL vial |
|---|---|---|---|---|
| Insulin glargine | 100 Units | 100 Units | 100 Units | 100 Units |
| *m*-Cresol | 2.7 mg | 2.7 mg | 2.7 mg | 2.7 mg |
| Polysorbate 20 | - | 20 µg | - | 20 µg |
| Glycerol (b) (4) w/w; | 20 mg | 20 mg | 20 mg | 20 mg |
| Zinc | 30 µg | 30 µg | 30 µg | 30 µg |
| Water for injection | Quantity sufficient | Quantity sufficient | Quantity sufficient | Quantity sufficient |

Source: BLA 761201, Module 3.2.P.2.2, Table 3.2.P.2.2/1

**Comments on Impurities of Concern**

There are no impurities or degradants of toxicological concern.

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## 5. Clinical Pharmacology Evaluation and Recommendations

### 5.1. Clinical Pharmacology Executive Summary and Recommendation

The Applicant conducted study MYL-1501D-1003 that compared the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of MYL-1501D in cartridges (formulation intended for pen presentations) compared to U.S.-licensed Lantus to support a demonstration of no clinically meaningful differences between MYL-1501D and U.S.-licensed Lantus in terms of safety, purity and potency. In addition, the Applicant provided Study MYL-1501-1004 that compared the PK and PD profiles of MYL-1501D in cartridges (formulation intended for pen presentations) with MYL-1501D in vials. Both studies were performed in healthy subjects. The study results provided an adequate time-concentration profile and time-action profile for each product based on reliable measures of systemic exposure and glucose response (glucose infusion rate), using an euglycemic clamp procedure.

The scientific basis for relying on the comparative PK and PD data between MYL-1501D and U.S.-licensed Lantus (in conjunction with the data and information from the CAA, including nonclinical *in vitro* assays), to support a demonstration of the biosimilarity and interchangeability of MYL-1501D with U.S.-licensed Lantus in this submission, is as follows:

- Demonstration that the molar dose ratio for MYL-1501D (test insulin product) is similar to U.S.-licensed Lantus (reference product) as determined based on on similarity in peak (Cmax) and total exposure (AUC0-24h) and the corresponding peak (GIRmax) and net glucose lowering effect (AUCGIR; from PD profiles (i.e., glucose infusion rate over time) from euglycemic clamp studies) between MYL-1501D, where both MYL-1501D and U.S. Lantus were formulated as 100 Units/mL or 600 nmol/mL, and when given as the same unit/kg SC dose (i.e. same injection volume for a unit dose)*.*
- Demonstration of similarity in the time-action profile between MYL-1501D and U.S.-licensed Lantus is on a unit to unit basis, i.e. MYL-1501D has the same unit dose definition, time to peak action and duration, which supports that MYL-1501D will be equally effective as U.S.-licensed Lantus.

The similarity data from the randomized, crossover design PK/PD study conducted for MYL-1501D and U.S.-licensed Lantus, supports a conclusion about whether there are no clinically meaningful differences between the treatments. In this submission, the demonstration of PK/PD similarity using the concept of average equivalence assessment for PK and PD parameters provides sufficient sensitivity for detecting clinically meaningful differences, should they exist, between MYL-1501D and U.S.-licensed Lantus.

**Table 4. Clinical Pharmacology Major Review Issues and Recommendations**

| Review Issue | Recommendations and Comments |
|---|---|
| **Pharmacokinetics** | • PK similarity was demonstrated between MYL-1501D and U.S.-Lantus in healthy subjects using the pre-filled pen formulation (also referred to as cartridge elsewhere in the review) (Study MYL-1501D-1003).<br>• PK comparability was demonstrated between MYL-1501D (vial formulation) and MYL-1501D (prefilled pen formulation) in healthy subjects (Study MYL-1501D-1004).<br>• The 90% confidence interval (CI) of the geometric least square mean ratio (GLSMR) for each product pairwise comparison for area under the concentration-time curve ($AUC_{0-24h}$), |

| | |
|---|---|
| | and maximum concentration ($C_{max}$) were within the PK similarity acceptance criteria of 80 to 125% (**Table 5**)**Error! Reference source not found.**.<br>• PK data from Study MYL-1501D-1003 and MYL-1501D-1004 support a demonstration of no clinically meaningful differences between MYL-1501D and U.S.-Lantus. |
| **Pharmacodynamics** | • PD similarity was demonstrated between MYL-1501D and U.S.-Lantus in healthy subjects (Study MYL-1501D-1003).<br>• PD comparability was demonstrated between MYL-1501D (vial formulation) and MYL-1501D (prefilled pen formulation) in healthy subjects (Study MYL-1501D-1004).The 90% CI of the GLSMR for each product pairwise comparison for AUC of glucose infusion rate (GIR) ($AUC_{GIR,0-24h}$), and maximum GIR ($GIR_{max}$) were within the PD similarity acceptance criteria of 80 to 125% (**Table 5**).<br>• PD data from Study 1003 and 1004 support a demonstration of no clinically meaningful differences between MYL-1501D and U.S.-Lantus. |
| **Immunogenicity** | • The single dose cross-over design of euglycemic clamp studies is appropriate for assessing PK/PD similarity, but not for evaluating immunogenicity. The limited immunogenicity data collected in MYL-1501D-1003 does not contribute meaningfully to the immunogenicity assessment of MYL-1501D. |

Under this 351(k) BLA submission, Mylan's MYL-1501D (manufactured using Process VI) is being proposed as an interchangeable biosimilar biological product to U.S.-licensed Lantus. To demonstrate that MYL-1501D is biosimilar to and interchangeable with U.S.-Lantus, the applicant submitted two clinical pharmacology studies, MYL-1501D-1003 and MYL-1501D-1004. The Clinical Pharmacology review focused on the PK/PD comparison of the MYL-1501D (Process VI) to U.S.-Lantus from Study 1003 (prefilled pen formulation comparison) and the PK/PD bridging between the vial and cartridge (the same formulation for the prefilled pen presentation) formulations for MYL-1501D (Process VI) from Study 1004.

Study MYL-1501D-1003 is a randomized, double-blind, single-dose, 3-treatment, 6-period, 6-sequence, fully replicated euglycemic glucose clamp study in healthy subjects designed to compare the PK and PD (i.e., glucose infusion rate [GIR]) profile of MYL-1501D (Process V), MYL-1501D (Process VI) and U.S.-Lantus following a single 0.5

Unit/kg body weight subcutaneous (SC) dose. The least-square geometric mean ratio (GMR) of the PK and PD parameters along with the 90% confidence intervals (CI) of all pairwise comparisons were within the prespecified margin of 80% to 125%. The results of the study established the PK and PD similarity between MYL-1501D (Process VI)) and U.S.-Lantus based on the primary PK endpoints of $C_{max}$ and $AUC_{0-24h}$, and PD endpoints of $GIR_{max}$ and $AUC_{GIR0-24h}$. Drug substances manufactured by Process VI were the drug substances for the to-be-marketed formulation. Therefore, data from MYL-1501D (Process VI) and U.S.-Lantus are reviewed to support PK and PD similarity between MYL-1501D and U.S.-Lantus. As described above, comparability of MYL-1501D Process V and MYL-1501D Process VI was supported by MYL-1501D-1003, along with analytical and additional clinical data. Data from MYL-1501D (Process V) are included here for completeness.

Study MYL-1501D-1004 is a randomized, double-blind, single-dose, 2-treatment, fully replicated 4-way crossover euglycemic glucose clamp study in healthy subjects designed to compare the PK and PD (i.e., GIR) profile of MYL-1501D (Process VI prefilled pen formulation) and MYL-1501D (Process VI vial formulation) following a 0.5 Unit/kg body weight subcutaneous (SC) dose. The least-square geometric mean ratio (GMR) of the PK and PD parameters along with the 90% confidence intervals (CI) of all pairwise comparisons were within the prespecified margin of 80% to 125%. The results of the study established the PK and PD comparability between MYL-1501D (Process VI prefilled pen formulation) and MYL-1501D (Process VI vial formulation) based on the primary PK endpoints of $C_{max}$ and $AUC_{0-24h}$ and PD endpoints of $GIR_{max}$ and $AUC_{GIR0-24h}$.

Overall, the results from Study MYL-1501D-1003 and Study MYL-1501D-1004 support the demonstration of no clinically meaningful differences between MYL-1501D (Process VI prefilled pen formulation), MYL-1501D (Process VI vial formulation) and US-Lantus in terms of safety, purity, and potency and add to the totality of the evidence to support a demonstration of biosimilarity between MYL-1501D (Process VI, vial or prefilled pen formulation) to U.S. Lantus.

**Table 5. Summary of statistical analyses for comparison of PK and PD parameters for Study Study MYL-1501D-1003 and Study MYL-1501D-1004**

| **Primary Parameter** | **Study 1003 - Geometric LS Mean Ratio (90% CI)** | **Study 1004 - Geometric LS Mean Ratio (90% CI)** |
|---|---|---|
| | **MYL-1501D (Process VI) vs. US- Lantus (prefilled pen formulation comparison)** | **MYL-1501D vial vs. prefilled pen formulation comparison** |
| PK (M1): | | |
| $AUC_{0-24h}$ (hr*ng/mL) | 99.08% (95.11-103.22%) | 97.94% (90.5-106.01%) |
| $C_{max}$ (ng/mL) | 99.63% (94.94-104.55%) | 97.92% (91.67-104.59%) |
| PD: | | |
| $AUC_{G\ R0-24h}$ (mg/kg) | 94.92% (86.95-103.62%) | 99.98% (93.95-106.39%) |
| $GIR_{max}$ (mg/kg/min) | 96.44% (89.33-104.11%) | 99.54% (93.51-105.95%) |

Source: Reviewer's analysis

### 5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

The clinical pharmacology studies adequately demonstrated PK and PD similarity of MYL-1501D vial or prefilled pen formulation with U.S.-Lantus. There are no residual uncertainties from the clinical pharmacology assessment.

## 5.2. Clinical Pharmacology Studies to Support the Use of a Non-U.S.-Licensed Comparator Product

Not applicable.

## 5.3. Human Pharmacokinetic and Pharmacodynamic Studies

To demonstrate that MYL-1501D is biosimilar to and interchangeable with U.S.-Lantus, the applicant submitted two clinical pharmacology studies, MYL-1501D-1003 and MYL-1501D-1004.

- Study MYL-1501D-1003: *A Glucose Clamp Study Investigating the Bioequivalence of MYL-1501D (Process V) and MYL-1501D (Process VI) with US Lantus® Reference Product in Healthy Volunteers*
- Study MYL-1501D-1004: *A glucose clamp trial investigating the bioequivalence of MYL-1501D formulation in vials versus MYL-1501D formulation in cartridges in healthy volunteers*

### 5.3.1. Study MYL-1501D-1003

#### Clinical Pharmacology Study Design Features

Study MYL-1501D-1003 was a randomized, double-blind, single-dose, three-treatment, six period, six sequence, fully replicated crossover design euglycemic glucose clamp study in healthy subjects. The PK and PD of MYL-1501D produced using two different manufacturing processes (Process V and Process VI) were compared to U.S.-Lantus.

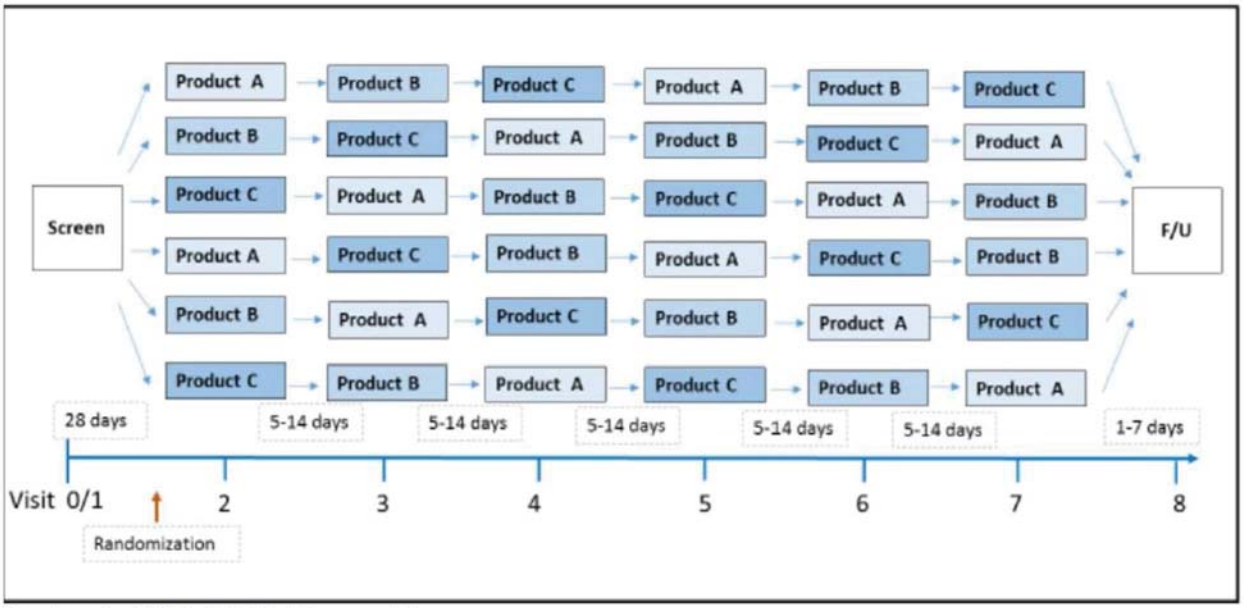
The study consisted of eight study visits (Figure 4): a Screening Visit (Visit 1), six Dosing Periods (Visits 2-7) during the Treatment Period, and a Follow-up Visit (Visit 8). There was a 5 to 14-day washout period between each of the Dosing Periods. Each Dosing Period included one 24-hour euglycemic glucose clamp (glucose clamp target: 81 mg/dL [4.45 mmol/L]) and was identical in procedure. PK, PD, and safety endpoints were assessed. The clamp setting was based on an automated glucose clamp technique with continuous blood glucose measurements (GlucoScout™, International Biomedical, TX) and adaptations of glucose infusion rates.

A total of 95 subjects were randomized, and 74 subjects (77.9%) completed the study. All of the enrolled subjects, 95 subjects, were included in the full analysis set (FAS) and the Safety Analysis Set. Seven subjects were excluded from the per-protocol population (PPP), 88 subjects, which included all subjects in the FAS who completed at least 2 periods of the study without any major protocol deviation. All subjects in the PPP were included in the PK and PD analysis with the following exceptions:

- For PK analysis, Subject [redacted] (b) (6)-Period 2, Subject [redacted] (b) (6)-Period 1, and Subject [redacted] (b) (6)-Period 3 were excluded due to pre-dose concentration greater than 5% Cmax or anomalous spikes in M1 concentrations within 2 hours after dosing

- For PD analysis: Subject [redacted] (b) (6)-all periods, Subject [redacted] (b) (6)-Period 1, Subject [redacted] (b) (6)-Period 4, and Subject [redacted] (b) (6)-Period 5 were not used for PD analysis due to poor quality of clamps data.

**Figure 1. Schematic overview of the chronological structure of Study MYL-1501D-1003**




Product A: MYL-1501D (Process V).
Product B: MYL-1501D (Process VI).
Product C: US Lantus (insulin glargine injection) (reference).
Source: Figure 1 of CSR MYL-1501D-1003

## Clinical Pharmacology Study Endpoints

In Study MYL-1501D-1003, the primary PK endpoints were area under the metabolite M1 concentration curve from 0 to 24 hours ($AUC_{0-24h}$) and maximum observed metabolite M1 concentration ($C_{max}$). Among study drug, M1 and M2, M1 is the major active analyte in plasma and therefore considered appropriate for the PK similarity assessment when the bioanalytical methods can specifically quantify all three analytes.

The primary PD endpoints were area under the glucose infusion rate curve from 0 to 24 hours ($AUC_{GIR.0-24h}$) and maximum glucose infusion rate ($GIR_{max}$).

To demonstrate similarity for PK and PD endpoints, the 90% CI of the geometric LS mean ratios need to fall within 80-125%.

**Bioanalytical PK Method and Performance**

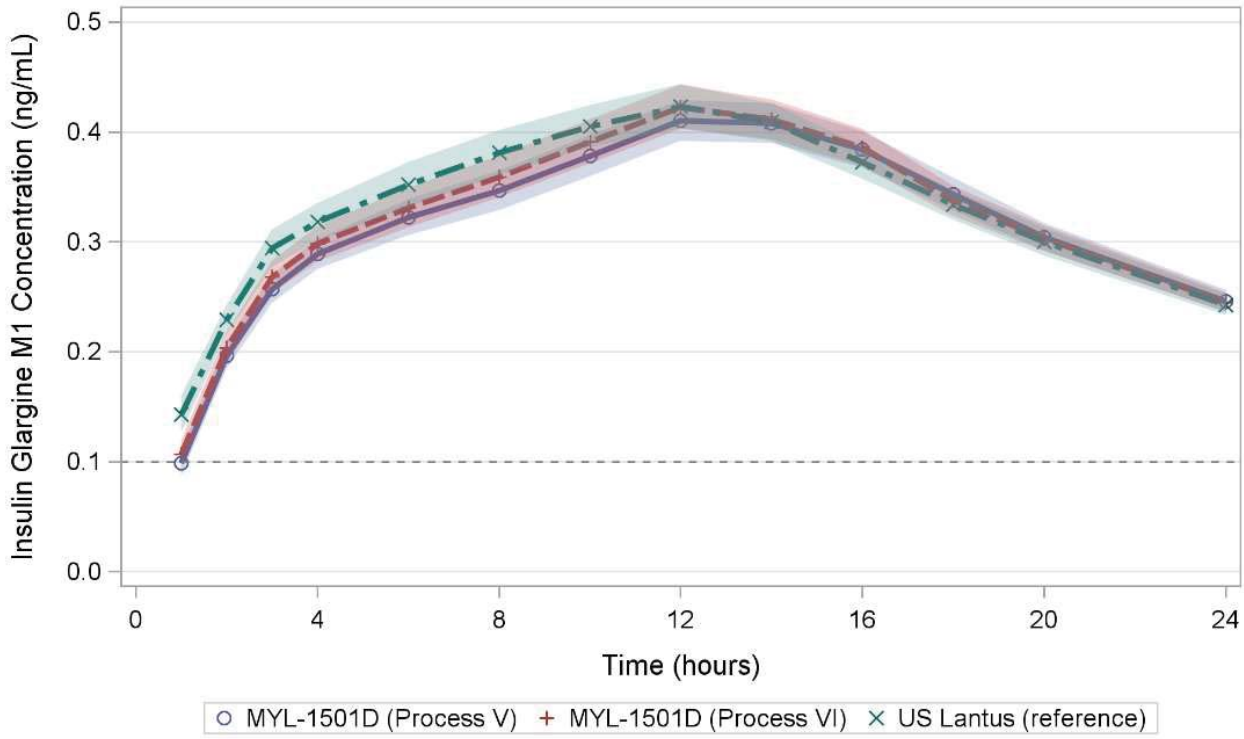
The bioanalytical method (GIA3HPP) for analysis of study drug, M1, M2 analytes in Study MYL-1501D-1003 employed an immunoaffinity extraction technique for sample preparation followed by tandem mass spectrometric detection (LC-MS/MS). The method was validated over a range of 0.1 to 1.5 ng/mL for all analytes. GIA3HPP was fully validated in accordance with the Bioanalytical Method Validation guidance from the agency. See detailed information about the assay validation in Appendix 13.4.1.

**PK Similarity Assessment**

For the primary PK parameters (AUC0-24h and Cmax of metabolite M1), the similarity criterion (90% CI of the geometric least-square mean ratio for test/reference within the limits 80.00% and 125.00%) was met in all the comparisons (**Table 5** and **Table 6**). Also for secondary PK parameters, the 90% CI of the GMR for test/reference lay within these limits (**Table 7**).

The results of the sensitivity analysis that included Subject (b) (6) Period 2, (b) (6) Period 1, and (b) (6) Period 3 who were excluded from the primary analyses due to either pre-dose concentration > 5% Cmax or having anomalous spikes in M1 concentrations within 2 hours after dosing also supported PK comparability/similarity between MYL-1501D (Process V), MYL-1501D (Process VI), and U.S.-Lantus (insulin glargine injection).

**Figure 2. Mean plasma M1 concentration versus time profiles by treatment in Study MYL-1501D-1003**




Note: Reference line at 0.1 ng/mL represents the LLOQ.
Source: Reviewer's Analysis using PPP excluding Subjec (b) (6) Period 2 (b) (6) Period 1, and (b) (6) Period 3.

**Table 6. Summary statistics of PK (M1) parameters in Study MYL-1501D-1003**

| Treatment | Parameter | Units | N | Mean | CV (%) | SD | Median | Minimum | Maximum |
|---|---|---|---|---|---|---|---|---|---|
| MYL-1501D (Process V) | AUC0-24h | ng.hr/mL | 87 | 7.57 | 31 | 2.4 | 7.3 | 3 | 14.6 |
| | Cmax | ng/mL | 87 | 0.45 | 35 | 0.2 | 0.4 | 0.2 | 1 |
| | Tmax | hr | 87 | . | . | . | 12 | 4 | 20 |
| MYL-1501D (Process VI) | AUC0-24h | ng.hr/mL | 86 | 7.7 | 31 | 2.4 | 7.5 | 3 | 19 |
| | Cmax | ng/mL | 86 | 0.46 | 35 | 0.2 | 0.4 | 0.2 | 1.2 |
| | Tmax | hr | 86 | . | . | . | 12 | 3 | 20 |
| US Lantus (Reference) | AUC0-24h | ng.hr/mL | 86 | 7.88 | 30 | 2.4 | 7.5 | 2.1 | 15.5 |
| | Cmax | ng/mL | 86 | 0.47 | 38 | 0.2 | 0.4 | 0.2 | 1.6 |
| | Tmax | hr | 86 | . | . | . | 12 | 3 | 20 |
| For Tmax- Only Median, Minimum, and Maximum are presented | | | | | | | | | |

Source: Reviewer's Analysis using PPP excluding Subject (b) (6) Period 2, (b) (6) Period 1, and (b) (6) Period 3.

**Table 7. Summary of statistical comparison of primary PK (M1) parameters in Study MYL-1501D-1003**

| Comparison | Primary PK Parameters | Units | Geometric LS Means (Trt A) | Geometric LS Means (Trt B) | Geometric LS Means (Trt C) | Ratio(%) | 90% CI |
|---|---|---|---|---|---|---|---|
| A vs. B | AUC0-24h | ng.hr/mL | 7.42 | 7.2 | 7.48 | 103.01 | 98.91 - 107.28 |
| | Cmax | ng/mL | 0.44 | 0.43 | 0.44 | 102.65 | 97.98 - 107.55 |
| A vs. C | AUC0-24h | ng.hr/mL | 7.42 | 7.2 | 7.48 | 99.08 | 95.11 - 103.22 |
| | Cmax | ng/mL | 0.44 | 0.43 | 0.44 | 99.63 | 94.94 - 104.55 |
| B vs. C | AUC0-24h | ng.hr/mL | 7.42 | 7.2 | 7.48 | 96.19 | 92.56 - 99.97 |
| | Cmax | ng/mL | 0.44 | 0.43 | 0.44 | 97.06 | 92.97 - 101.32 |
| Trt A = MYL-1501D (Process VI)<br>Trt B = MYL-1501D (Process V)<br>Trt C = US Lantus (Reference) | | | | | | | |

Source: Reviewer's Analysis using PPP excluding Subjec (b) (6) Period 2, (b) (6) Period 1, and (b) (6) Period 3.

## Bioanalytical PD Measurement Method and Performance

The euglycemic clamp technique was used to measure PD response. In this technique glucose is administered intravenously as to counter the glucose lowering effect of MYL-1501D and U.S.-Lantus in order to maintain the plasma glucose (thus the name euglycemia). The temporal profile of glucose-infusion rate over time serves as the PD response measure.

In Study MYL-1501D-1003, there was a 24-hour euglycemic clamp for each dosing period. Each clamp includes a 60-minute stabilization period and target glucose value of 81 mg/dL (4.45 mmol/L).

The glucose clamp procedure was carried out using the automated ClampArt (Profil) device. ClampArt glucose measurements were double-checked with the real-time glucose measurments through Super GL analyzer at least every 30 minutes and adjusted if necessary.

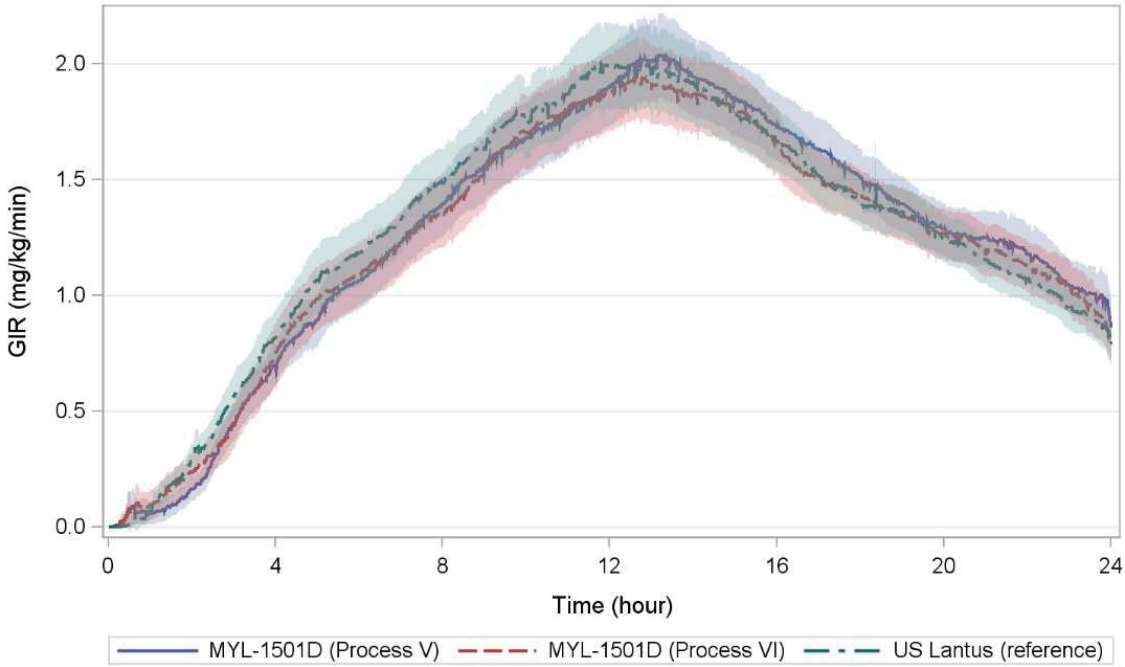
We found the overall clamp methodology acceptable based on the glucose control data included with the study results. See appendix 14.4.1 for more details.

C-peptide concentrations in serum samples from Study 1003 were measured by an accredited CLIA/CAP lab.

## PD Similarity Assessment

Figure 3 below shows the mean (90%CI) GIR versus time profile by treatment. On average, the PD response as assessed by GIR over time was consistent between MYL-1501D (Process VI), MYL-1501D (Process V) and U.S.-Lantus.

**Figure 3. Mean GIR versus time profile by treatment in Study MYL-1501D-1003**




Source: Reviewer's analysis using PPP excluding Subject [redacted] (b) (6) Period 1, [redacted] (b) (6) Period 4, and [redacted] (b) (6) Period 5.

**Table 8. Summary statistics PD parameters in Study MYL-1501D-1003**

| Treatment | Parameter | Units | N | Mean | CV (%) | Median | Minimum | Maximum |
|---|---|---|---|---|---|---|---|---|
| MYL-1501D (Process V) | GIRAUC0-24h | mg/kg | 86 | 1780.47 | 65 | 1495.9 | 0 | 5400.5 |
| | GIRmax | mg/kg/min | 86 | 2.27 | 62 | 1.86 | 0 | 7.15 |
| | TGIRmax | hr | 85 | . | . | 14 | 1 | 24 |
| MYL-1501D (Process VI) | GIRAUC0-24h | mg/kg | 85 | 1758.15 | 66 | 1523.6 | 0 | 6385.3 |
| | GIRmax | mg/kg/min | 85 | 2.18 | 61 | 1.85 | 0 | 6.51 |
| | TGIRmax | hr | 84 | . | . | 13 | 2 | 24 |
| US Lantus (Reference) | GIRAUC0-24h | mg/kg | 85 | 1808.51 | 61 | 1632.7 | 0 | 4841.7 |
| | GIRmax | mg/kg/min | 85 | 2.26 | 60 | 1.91 | 0 | 6.31 |
| | TGIRmax | hr | 84 | . | . | 13 | 4 | 24 |
| For TGIRmax- Only Median, Minimum, and Maximum are presented | | | | | | | | |

Source: Reviewer's Analysis using PPP excluding Subject [redacted] (b) (6) Period 1, [redacted] (b) (6) Period 4, and [redacted] (b) (6) Period 5.

For the PD parameters, the acceptance criterion (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in both comparisons for the primary PD parameters (AUCGIR0-24h and GIRmax) (**Error! Reference source not found.** and Table 9).

**Table 9. Treatment comparisons of primary PD parameters in Study MYL-1501D-1003**

| Comparison | Primary PD Parameters | Units | Geometric LS Means (Trt A) | Geometric LS Means (Trt B) | Geometric LS Means (Trt C) | Ratio(%) | 90% CI |
|---|---|---|---|---|---|---|---|
| A vs. B | GIRAUC0-24h | mg/kg | 1396.32 | 1359.15 | 1471.04 | 102.73 | 94.02 - 112.26 |
| | GIRmax | mg/kg/min | 1.84 | 1.85 | 1.91 | 99.81 | 92.78 - 107.37 |
| A vs. C | GIRAUC0-24h | mg/kg | 1396.32 | 1359.15 | 1471.04 | 94.92 | 86.95 - 103.62 |
| | GIRmax | mg/kg/min | 1.84 | 1.85 | 1.91 | 96.44 | 89.33 - 104.11 |
| B vs. C | GIRAUC0-24h | mg/kg | 1396.32 | 1359.15 | 1471.04 | 92.39 | 84.89 - 100.56 |
| | GIRmax | mg/kg/min | 1.84 | 1.85 | 1.91 | 96.62 | 90.33 - 103.35 |

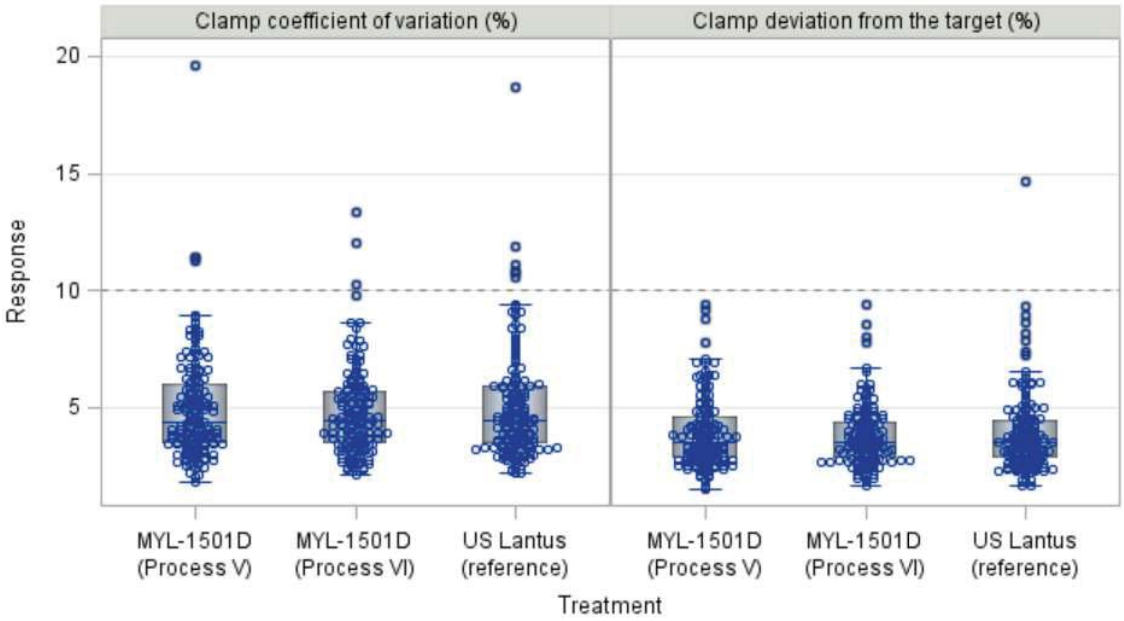
Trt A = MYL-1501D (Process VI)
Trt B = MYL-1501D (Process V)
Trt C = US Lantus (Reference)

Source: Reviewer's Analysis using PPP excluding Subject (b) (6) Period 1, (b) (6) Period 4, and (b) (6) Period 5.

The results of the sensitivity analyses performed using a clamp CV and deviation from target (DFT) constraint, and C-peptide constraints supported PD similarity between MYL-1501D (Process VI), MYL-1501D (Process V) and U.S.-Lantus (insulin glargine injection).

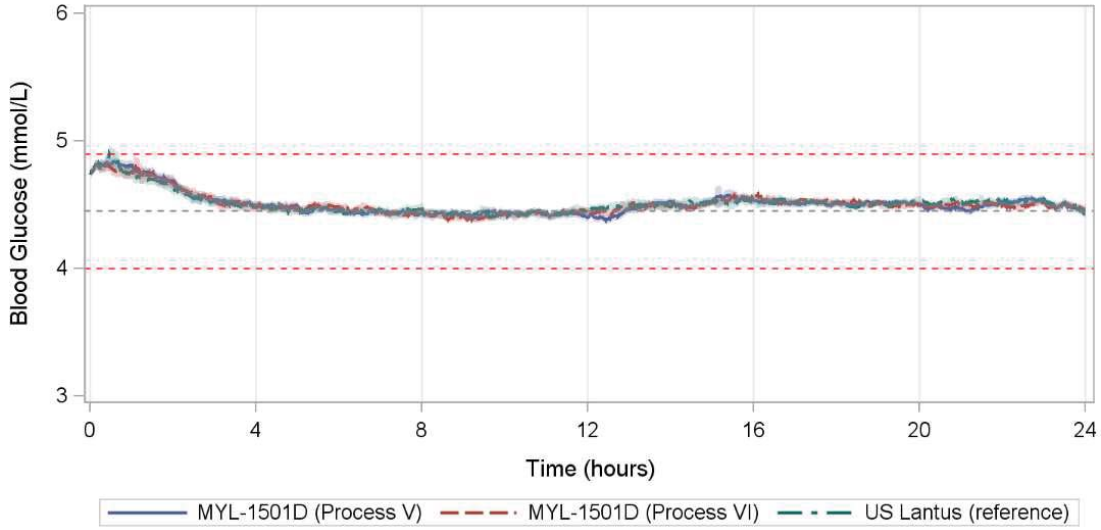
The euglycemic clamp quality were assessed through assessment of coefficient of variation of blood glucose during clamp and percent deviation from the target glucose data. **Figure 5.** and **Figure 6.** below present the graphical comparison of clamp quality metrics and blood glucose during clamp duration, the latter being consistently within ±10% of the euglycemic target for both treatments. In addition, C-peptide (i.e., a breakdown product of endogenous pro-insulin) was also similarly suppressed during the clamp duration among treatment groups (**Figure 6**) indicating minimal confounding of the PD response by the endogenous insulin.

**Figure 4. Comparison of clamp quality metrics in Study MYL-1501D-1003**



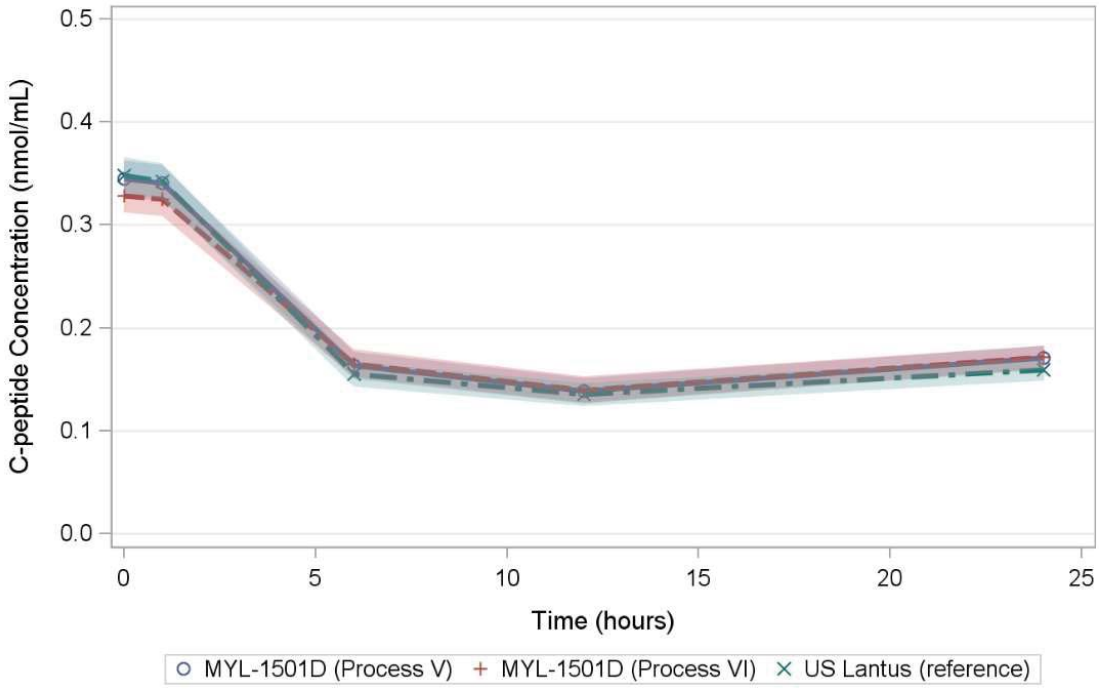

Source: Reviewer's Analysis including all subjects

**Figure 5. Mean blood glucose concentrations during clamp by treatment in Study MYL-1501D-1003**




Note: Reference line at 4.45 mmol/L is target blood glucose; reference lines in red indicate +/- 10% of the euglycemic clamp target; glucose data converted to mmol/l as 1 mg/dL = 0.055 mmol/L.
Source: Reviewer's Analysis including all subjects

**Figure 6. Mean plasma C-peptide concentrations during clamp by treatment**




Source: Reviewer's Analysis including all subjects

### 5.3.2. Study MYL-1501D-1004

**Clinical Pharmacology Study Design Features**

Study MYL-1501D-1004 was a two-center, randomized, double-blind, 4-way crossover, fully replicated, 2-treatment study comparing single doses of MYL-1501D Process VI in vial with polysorbate with MYL-1501D Process VI in cartridges without polysorbate in healthy subjects.

In total 48 subjects (20 at trial site Neuss and 28 at trial site Mainz) were randomized to one of the 2 treatment sequences and 45 completed the trial. Three (3) subjects (6.3%) prematurely discontinued trial participation after randomization and at least 1 dose administration, all on own initiative. Each completer participated in 7 visits (**Error! Reference source not found.**): an informed consent visit (at least one day before Visit 1), a screening visit (Visit 1, 1 to 28 days before Visit 2) to check eligibility for participation, 4 dosing visits (Visits 2, 3, 4 and 5, separated by a washout period of 5 to 21 days), and a follow-up visit with final examination (Visit 6, 1 to 10 days after Visit 5).

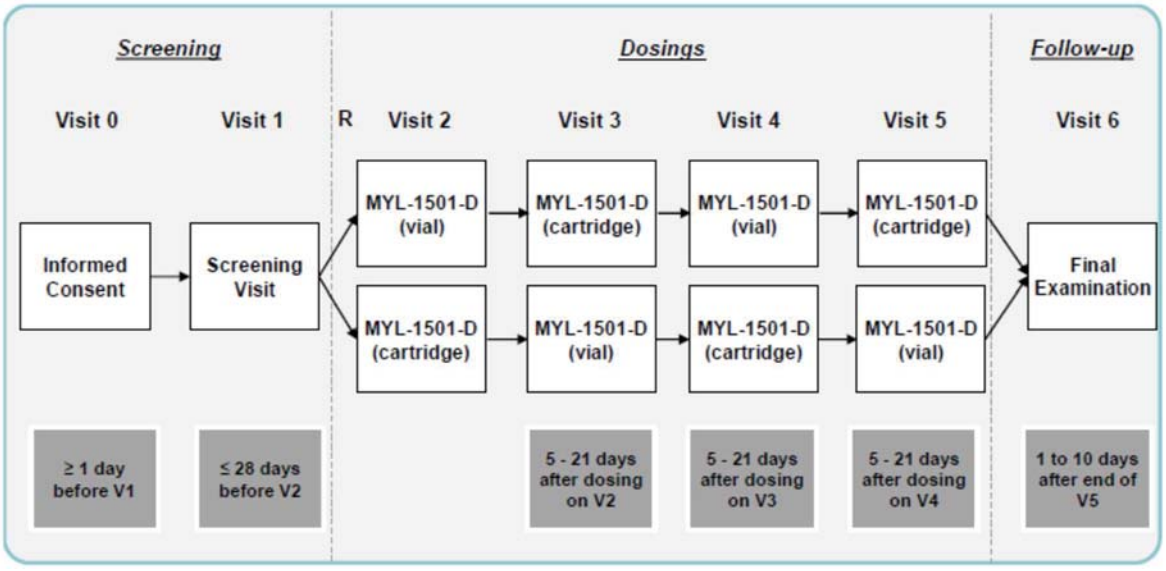
At Visits 2, 3, 4 and 5, the products were administered in 2 randomly allocated sequences in the setting of a 24-hour computer-controlled euglycemic glucose clamp (glucose clamp target: 81 mg/dL [4.45 mmol/L]). During the clamp procedure, blood was collected pre-dose and at pre-specified intervals until 24 hours post-dose for measurement of blood glucose (for verifying ClampArt measurements) and metabolite - M1. Safety assessments included vital signs recording, electrocardiograms (ECGs),

laboratory safety parameters, physical examination, and recording of adverse events (AEs).

The 45 completers of the trial were included in the PPP for PD. For the PPP for PK, additional 5 subjects subjects were excluded due to rules outlined in the SAP: They lacked any evaluate PK dosing period (R1 and R2) per treatment (vial or cartridge) due to less than 7 (50%) post-dosing PK measurements above LLOQ. The PPP population for PK comprised 40 subjects.

Among the 40 subjects included in the PK analysis (ideally expected to generate 80 PK observations per treatment due to fully replicated design), a total of 70 and 72 PK profiles for vial and cartridge treatments, respectively, were included in the statistical analysis of primary PK parameters ($AUC_{0\text{-}24h}$ and Cmax) due to each of the 40 subjects having at least having 1 observation per treatment. The number of PK profiles excluded was balanced for both treatments (10 and 8 PK profiles excluded for vial and cartridges, respectively).

**Figure 7. Schematic overview of the chronological structure of Study MYL-1501D-1004**




Source: Figure 1 of CSR MYL-1501D-1004

## Clinical Pharmacology Study Endpoints

In Study MYL-1501D-1004, the primary PK endpoints were area under the metabolite M1 concentration curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) and Maximum observed metabolite M1 concentration ($C_{max}$). Among study drug, M1 and M2, M1 is the major active analyte in plasma and therefore considered appropriate for the PK similarity assessment when the bioanalytical methods can specifically quantify all three analytes. The primary PD endpoints were area under the glucose infusion rate curve from 0 to 24 hours ($AUC_{GIR.0\text{-}24h}$) and maximum glucose infusion rate ($GIR_{max}$).

To demonstrate similarity for PK and PD endpoints, the 90% CI of Geometric LS mean ratios need to fall within 80-125%.

### Bioanalytical PK Method and Performance

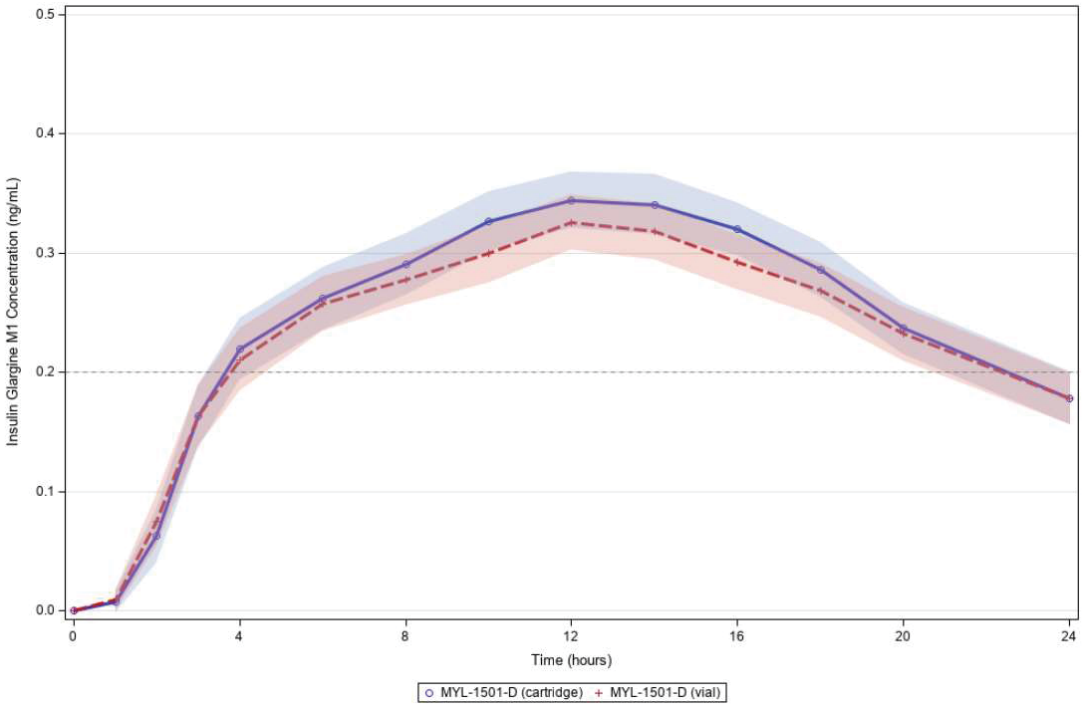
The bioanalytical method for Study MYL-1501D-1004, GLA3HPP Version 001, utilized a solid phase extraction technique for sample preparation followed by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). The method was validated over a range from 0.2 ng/mL to 3.0 ng/mL for all analytes. See detailed information about the assay validation in Appendix 13.4.1.

### PK Comparability Assessment

**Figure 8** shows the mean (90% CI) plasma MYL-1501D concentration versus time profiles of single doses of the two MYL-1501D formulations in healthy volunteers. Upon SC injection of 0.5 unit/kg, maximum plasma concentrations occurred at about 12 hours post-dose for the two MYL-1501D formulations and then decline to about 20 hours near quantitation limit. In general, the mean plasma concentration versus time profiles of the two MYL-1501D formulations appear comparable.

For the primary PK parameters (AUC0-24h and Cmax of metabolite M1), the acceptance criterion (90% CI of the geometric least-square mean ratio for test/reference within the limits 80.00% and 125.00%) was met in all the comparisons (**Table 10 Error! Reference source not found.**and **Table 11**).

**Figure 8. Mean (90% CI) plasma M1 concentration versus time profiles following single 0.5 unit/kg SC doses of the two MYL-1501D formulations in Study MYL-1501D-1004**



Note: Reference line at 0.2 ng/mL represents the LLOQ.
Source: Reviewer's analysis using PPP.

**Table 10. Summary statistics PK (M1) parameters in Study MYL-1501D-1004**

| Treatment | Parameter | Units | N | Mean | CV (%) | SD | Median | Minimum | Maximum |
|---|---|---|---|---|---|---|---|---|---|
| MYL-1501-D (cartridge) | AUC0-24h | ng.hr/mL | 40 | 6.38 | 31 | 1.98 | 6.29 | 3.24 | 14.1 |
| | Cmax | ng/mL | 40 | 0.4 | 27 | 0.11 | 0.39 | 0.23 | 0.87 |
| | Tmax | hr | 40 | . | . | . | 13 | 6 | 24 |
| MYL-1501-D (vial) | AUC0-24h | ng.hr/mL | 40 | 6.24 | 28 | 1.72 | 6.02 | 2.92 | 11.71 |
| | Cmax | ng/mL | 40 | 0.39 | 23 | 0.09 | 0.38 | 0.24 | 0.68 |
| | Tmax | hr | 40 | . | . | . | 12 | 3 | 20 |
| For Tmax - Only Median, Minimum, and Maximum are presented | | | | | | | | | |

Source: Reviewer's analysis using PPP.

**Table 11. Treatment comparisons of PK (M1) parameters in Study MYL-1501D-1004**

| Comparison | Primary PK Parameters | Units | Geometric LS Means (Test) | Geometric LS Means (Reference) | Ratio(%) | 90% CI |
|---|---|---|---|---|---|---|
| T vs. R | AUC0-24h | ng.hr/mL | 5.94 | 6.07 | 97.94 | 90.5 - 106.01 |
| | Cmax | ng/mL | 0.38 | 0.39 | 97.92 | 91.67 - 104.59 |
| Test (T) = MYL-1501-D (vial)<br>Reference (R)= MYL-1501-D (cartridge) | | | | | | |

Source: Reviewer's analysis using PPP.

## Bioanalytical PD Method and Performance

The euglycemic clamp technique was used to measure PD response. In this technique glucose is administered intravenously as to counter the glucose lowering effect of MYL-1501D in order to maintain the plasma glucose (thus the name euglycemia). The temporal profile of glucose-infusion rate over time serves as the PD response measure for MYL-1501D.

In Study MYL-1501D-1004, there was a 24-hour euglycemic clamp for each dosing period. Each clamp includes a 60-minute stabilization period and target glucose value of 81 mg/dL (4.45 mmol/L).

The glucose clamp procedure was carried out using the automated ClampArt (Profil) device. ClampArt glucose measurements were double-checked with the real-time glucose measurments through Super GL analyzer at least every 30 minutes and adjusted if necessary.

We found the overall clamp methodology acceptable. See appendix 13.4.1 for more details. C-peptide concentrations in serum samples from Study 1004 were measured by

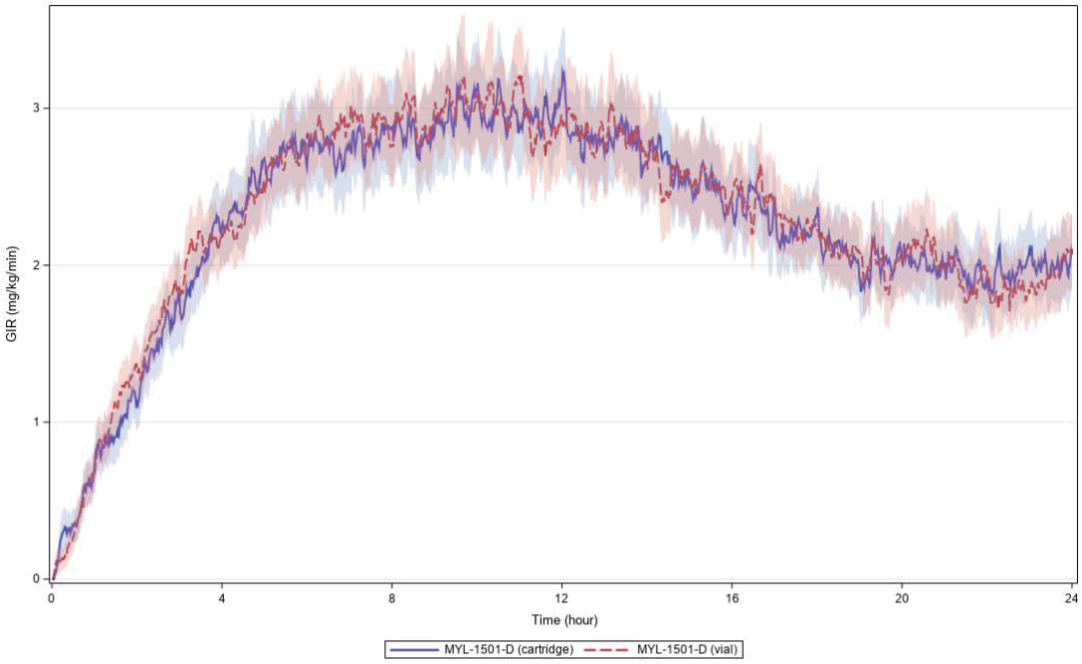
a locoal lab using a commercial kit assay from Roche Diagnostics. We found the validation reports are acceptable.

### PD Comparability Assessment

**Figure 9** below shows the mean (90%CI) GIR versus time profile by treatment. On average, the PD response as assessed by GIR over time was consistent between MYL-1501D Process VI in vial (with polysorbate) and MYL-1501D Process VI in cartridges (without polysorbate).

For the primary PD parameters (AUCGIR0-24h and GIRmax), the acceptance criterion (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in both comparisons (**Table 12** and **Table 13**).

**Figure 9. Mean (90% CI) GIR versus time profiles following single 0.5 unit/kg SC doses of the two MYL-1501D formulations in Study MYL-1501D-1004**




Source: Reviewer's analysis using PPP.

**Table 12. Summary statistics of primary PD endpoints in Study MYL-1501D-1004**

| Treatment | Parameter | Units | N | Mean | CV (%) | SD | Median | Minimum | Maximum |
|---|---|---|---|---|---|---|---|---|---|
| MYL-1501-D (cartridge) | GIRAUC0-24h | mg/kg | 45 | 54.76 | 48 | 26.51 | 49.67 | 11.04 | 129.97 |
| | GIRmax | mg/kg/min | 45 | 3.52 | 48 | 1.7 | 3.28 | 0.75 | 9.3 |
| | TGIRmax | hr | 45 | . | . | . | 11 | 4 | 24 |
| MYL-1501-D (vial) | GIRAUC0-24h | mg/kg | 45 | 54.59 | 49 | 26.63 | 51.09 | 14.13 | 134.62 |
| | GIRmax | mg/kg/min | 45 | 3.49 | 50 | 1.73 | 3.16 | 1.26 | 10.22 |
| | TGIRmax | hr | 45 | . | . | . | 10 | 3 | 24 |
| For TGIRmax- Only Median, Minimum, and Maximum are presented | | | | | | | | | |

Source: Reviewer's analysis using PPP

**Table 13. Treatment comparisons of PD parameters in Study MYL-1501D-1004**

| Comparison | Primary PD Parameters | Units | Geometric LS Means (Test) | Geometric LS Means (Reference) | Ratio(%) | 90% CI |
|---|---|---|---|---|---|---|
| T vs. R | GIRAUC0-24h | mg/kg | 48.38 | 48.39 | 99.98 | 93.95 - 106.39 |
| | GIRmax | mg/kg/min | 3.12 | 3.13 | 99.54 | 93.51 - 105.95 |
| Test (T) = MYL-1501-D (vial)<br>Reference (R) = MYL-1501-D (cartridge) | | | | | | |

Source: Reviewer's analysis using PPP

The quality of CLAMP for Study MYL-1501D-1004 was evaluated using:

1. Visual inspection of the individual clamp blood glucose profile (as measured by the ClampArt device)
2. Clamp coefficient of variation (CV in %), derived as 100 *(SD of blood glucose measured by ClampArt/ mean blood glucose measured by ClampArt)
3. Clamp deviation from Target (DFT), derived as Mean (blood glucose measured by ClampArt minus targeted clamp level, i.e., 81 mg/dL)

**Table 14. Summary Statistics of Quality of Clamp Data in Study MYL-1501D-1004**

| Parameter | Treatment | N Obs | Mean | SD | Min | Median | Max |
|---|---|---|---|---|---|---|---|
| CV% | MYL-1501D (vial) | 90 | 4.55 | 1.933 | 1.7 | 4.29 | 14.5 |
| | MYL-1501D (cartridge) | 90 | 4.80 | 1.492 | 2.2 | 4.49 | 9.9 |
| DFT [mg/dL] | MYL-1501D (vial) | 90 | 0.03 | 0.489 | -0.6 | -0.06 | 3.4 |
| | MYL-1501D (cartridge) | 90 | 0.03 | 0.367 | -0.6 | -0.06 | 1.7 |

Source: Applicant's analysis, Table 16 of Study MYL-1501-1004 Report Body

In general, the individual clamp blood glucose profiles were maintained within ± 15% of the targeted clamp level with no obvious deviation (**Table 14**).

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# 6. Statistical and Clinical Evaluation and Recommendations

## 6.1. Statistical and Clinical Executive Summary and Recommendation

The Applicant performed study MYL-1501D-3003 to address the regulatory requirements for interchangeability. The Applicant designed Study MYL-1501D-3003 as a switching study using recommendations described in FDA's May 2019 Guidance, *Considerations in Demonstrating Interchangeability With a Reference Product*.[12] As described in the Guidance, the primary endpoint in a switching study or studies should assess the impact of switching or alternating between use of the proposed interchangeable product and the reference product on clinical PK and PD (if available). This type of study would be expected to descriptively assess immunogenicity and safety.

The Applicant's design of study MYL-1501D-3003 was inadequate to support a demonstration of interchangeability between MYL-1501D and U.S.-Lantus. FDA did not agree with the Applicant's study design. As discussed in **Section 2.1**, FDA and the Applicant agreed at the October 2018 BPD Type 2 meeting that the primary endpoint of HbA1c alone is insufficiently sensitive to assess the impact of switching to support a demonstration of interchangeability.

FDA updated its scientific thinking regarding whether and when comparative clinical immunogenicity studies may be needed to support licensure of proposed biosimilar and interchangeable insulin products. FDA's updated thinking was outlined in the November 2019 *Insulin Immunogenicity Guidance*. This draft guidance stated a comparative clinical immunogenicity study generally would be considered unnecessary to support a demonstration of biosimilarity in a 351(k) BLA for a proposed insulin product seeking licensure as a biosimilar or interchangeable if the BLA contains a robust and comprehensive comparative analytical assessment demonstrating that the proposed insulin product is "highly similar" to its proposed reference product with very low residual uncertainty regarding immunogenicity and the application otherwise meets the standards for licensure under section 351(k) of the PHS Act.

With regard to proposed interchangeable products, as described in the guidance for industry Considerations in Demonstrating Interchangeability With a Reference Product (May 2019), advances in analytics may allow for extended analytical characterization that affects the extent of other data and information needed to support a demonstration

[12] Food and Drug Administration. Guidance for Industry: Considerations in Demonstrating Interchangeability With a Reference Product, May 2019, accessed from: https://www.fda.gov/media/124907/download

of interchangeability and may in certain circumstances lead to a more selective and targeted approach to clinical studies intended to support a demonstration of interchangeability. Consistent with these statements in the guidance and the recommendations in this section, a comprehensive and robust comparative analytical assessment between a proposed interchangeable insulin product and the reference product demonstrating that the proposed interchangeable product is “highly similar” to the reference product with very low residual uncertainty about immunogenicity generally would mean that an applicant would not need to conduct a comparative clinical immunogenicity study, e.g., a switching study, to support licensure under section 351(k)(4) of the PHS Act so long as the statutory criteria for licensure as an interchangeable are otherwise met.

The guidance recommended that a 351(k) BLA for a biosimilar or interchangeable insulin product contain, among other things, an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity.

Consistent with the *Insulin Immunogenicity Guidance*, the Applicant performed a comprehensive and robust comparative analytical assessment of MYL-1501D and U.S.-Lantus and submitted an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity was not necessary to support a demonstration of biosimilarity. The former adequately supported a demonstration that MYL-1501D is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive components. The results are summarized in **Section 3.1**. The latter adequately justified why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity. The assessment is discussed in **Section 6.4**. Based on the comparative analytical assessment findings and adequate immunogenicity assessment, FDA has determined that there is little or no residual uncertainty regarding immunogenicity of MYL-1501D and did not rely on study MYL-1501D-3003 to support a demonstration of interchangeability. Consequently, data from MYL-1501D-3003 are not necessary to support a demonstration of interchangeability. Because Study MYL-1501D-3003 was not necessary in this 351(k) application, it is discussed further in an appendix rather than in the body of the Biosimilar Multidisciplinary Evaluation and Review (BMER).

Overall, the immunogenicity assessment submitted in this application contributes to the totality of evidence supporting a demonstration of no clinically meaningful differences between MYL-1501D and US-Lantus in terms of safety, purity, and potency.

### 6.1.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties from the clinical perspective that would impact a demonstration of biosimilarity or interchangeability between MYL-1501D and U.S.-Lantus.

## 6.2. Review of Comparative Clinical Studies with Statistical Endpoints

One of the comparative clinical studies that was submitted (Study MYL-1501D-3003) constituted clinical data not previously reviewed by FDA. For that reason, Study MYL-1501D-3003 was reviewed to confirm that its results did not preclude or conflict with conclusions based on other sources of data and information. Because Study MYL-1501D-3003 was not necessary in this 351(k) application, it is discussed in **Appendix 13.5.1** rather than in this section of the Biosimilar Multidisciplinary Evaluation and Review (BMER).

## 6.3. Review of Safety Data

Study MYL-1501D-1003 and Study MYL-1501D-1004 were euglycemic clamp PK/PD studies; the designs of the studies are presented in **Section 5.3.1** and **Section 5.3.2**, respectively. Euglycemic clamp studies provide time-concentration profiles and time-action profiles based on reliable measures of systemic exposure and glucose response. The studies collected a limited amount of safety data during their conduct, but the safety data collected were not necessary to the demonstration of biosimilarity between MYL-1501D and U.S.-Lantus. The comparative analytical data and the results of study MYL-1501D-1003 and study MYL-1501D-1004 demonstrating PK and PD similarity between MYL-1501D and U.S.-Lantus support a demonstration of no clinically meaningful differences between MYL-1501D and U.S.-Lantus in terms of safety, purity, and potency, without reliance on safety data generated by study MYL-1501D-1003 and study MYL-1501D-1004. The limited amount of safety data that were collected during the conduct of study MYL-1501D-1003 and study MYL-1501D-1004 were inspected only to ensure that these data did not conflict with the conclusion of biosimilarity based on the analysis of the comparative analytical data and the finding of PK and PD similarity between MYL-1501D and U.S.-Lantus. Review of these limited safety data collected did not suggest any differences in the safety profiles of MYL-1501D and U.S.-Lantus.

One of the comparative clinical studies that was submitted (Study MYL-1501D-3003) constituted new clinical data not previously reviewed by FDA. For that reason, Study MYL-1501D-3003 was reviewed to confirm that its results did not preclude or conflict with conclusions based on other sources of data and information. Because Study MYL-1501D-3003 was not necessary in this 351(k) application, the safety data from MYL-1501D-3003 is discussed in **Appendix sections 13.5.2, 13.5.3, and 13.5.4** rather than in this section of the Biosimilar Multidisciplinary Evaluation and Review (BMER).

## 6.4. Clinical Conclusions on Immunogenicity

Consistent with the *Insulin Immunogenicity Guidance*, the Applicant submitted an immunogenicity assessment justifying why a comparative clinical immunogenicity study was not necessary to support a demonstration of biosimilarity for MYL-1501D.

The OPQ review concluded that the data provided by the Applicant, including the comparative analytical assessment, are adequate to support the conclusion that the manufacture of MYL-1501D is well controlled and leads to a product that is safe, pure, and potent and supported a demonstration that MYL-1501D is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive components.

In the immunogenicity assessment, the Applicant referenced the results of their comprehensive clinical program including the PK/PD studies and the four additional clinical studies (MYL-GAI-3001, MYL-GAI-3002, MYL-1501D-3003, and MYL-1501D-3004). The assessment included a summary of the results from the pre-specified immunogenicity analyses performed on each of the four clinical studies, a summary of the results from the post-hoc analyses performed on those studies using a treatment emergent antibody response (TEAR) approach, and a reference to the efficacy and safety findings from the studies.

The Agency does not agree with all of the arguments presented in the Applicant's immunogenicity assessment, including various assessments derived from data from MYL-GAI-3001, MYL-GAI-3002, MYL-1501D-3003, and MYL-1501D-3004 . However, the Applicant does present information that comprises an adequate justification for why a comparative clinical study to assess immunogenicity is not necessary to support a demonstration of biosimilarity. The Applicant's comparative analytical assessment demonstrates that MYL-1501D is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive components. In addition, the FDA review of PK/PD studies MYL-1501D-1003 and MYL-1501D-1004 concluded that the Applicant was able to demonstrate PK and PD similarity between MYL-1501D and U.S.-Lantus. In conjunction with the CAA, these results support a demonstration that there are no clinically meaningful differences between MYL-1501D and U.S.-Lantus. Finally, although the results from studies MYL-GAI-3001, MYL-GAI-3002, and MYL-1501D-3003[13] were unnecessary to demonstrate that there are no clinically meaningful differences between MYL-1501D and U.S.-Lantus, the results from these studies do not preclude or conflict with that conclusion. Therefore, there is no residual uncertainty regarding immunogenicity from a clinical perspective.

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[13] As noted above, study MYL-1501D-3004, along with additional data and information, supported the demonstration of comparability between Process V and Process VI, as the applicant's analytical data included materials manufactured using both Process V and Process VI

## 6.5. Risk in Terms of Safety or Dimished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant has developed MYL-1501D as a proposed interchangeable biosimilar to U.S.-Lantus and is seeking licensure of MYL-1501D for the same indication, same dosage form, strengths, and route of administration as U.S.-Lantus.

The Applicant submitted data and information from a comprehensive and robust comparative analytical assessment between MYL-1501D and U.S.-Lantus demonstrating that MYL-1501D is highly similar to U.S.-Lantus, notwithstanding minor differences in clinically inactive components. Additionally, the Applicant submitted data from Study 1003, a PK/PD study conducted in healthy subjects that provided a time-concentration profile and a time-action profile over the duration of MYL-1501D and U.S.-Lantus based on reliable measures of systemic exposure and glucose response using a euglycemic clamp procedure. Study 1003 demonstrated PK and PD similarity between MYL-1501D and U.S.-Lantus. Given the foregoing as well as the determination described above that the immunogenicity assessment was adequate, and consistent with the principles in the *Insulin Immunogenicity Guidance*, a comparative clinical immunogenicity study is not necessary to support the demonstration of interchangeability.[14]

As explained above, the known and potential mechanisms of action of insulin products, including U.S.-Lantus, include the regulation of glucose metabolism. Insulin and insulin analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Comparative analytical testing, including multiple orthogonal assays relevant to the mechanism of action of U.S.-Lantus, plus comparative clinical pharmacodynamic data evaluating glucose metabolism, demonstrated that MYL-1501D has the same mechanism(s) of action as that of U.S.-Lantus, to the extent known. Healthy subjects comprise an adequately sensitive population in which to evaluate PK and PD similarity via a euglycemic clamp experiment (which allows the measurement of insulin pharmacokinetics and pharmacodynamic response without risk of hypoglycemia).

U.S.-Lantus has two presentations: a 10 mL multiple-dose vial and a 3 mL single-patient-use pre-filled pen (PFP), and the Applicant is seeking licensure of both a 10 mL multi-dose vial and a 3 mL PFP. There are no residual uncertainties from a device or medication error perspective that would preclude a demonstration of interchangeability.

The totality of evidence demonstrates that MYL-1501D is biosimilar to U.S.-Lantus. In addition, the totality of evidence submitted in the application sufficiently demonstrates that MYL-1501D can be expected to produce the same clinical results as U.S.-Lantus in any given patient and that, the risk in terms of safety or diminished efficacy of

[14] The results of the comparative clinical studies, were supportive of, but not necessary, to the demonstration of biosimilarity and interchangeability.

alternating or switching between use of MYL-1501D and U.S.-Lantus is not greater than the risk of using U.S.-Lantus without such alteration or switch.

## 6.6. Extrapolation

### 6.6.1. Division of Diabetes, Lipid Disorders, and Obesity

The information submitted in the application, including the comparative analytical data and the PK/PD results (which together demonstrate that the mechanism of action is the same in MYL-1501D and U.S.-Lantus, to the extent known) supports a demonstration that MYL-1501D and U.S.-Lantus are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of safety, purity, and potency. The information in the BLA also supports a demonstration that MYL-1501D can be expected to produce the same clinical result as U.S.-Lantus in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of MYL-1501D and U.S.-Lantus is not greater than the use of U.S.-Lantus without such switch or alternation. An extrapolation of the finding of PK similarity of MYL-1501D and U.S.-Lantus in healthy adults to adult patients with T1DM, pediatric patients with T1DM, and adult patients with T2DM is justified because the same scientific factors that determine absorption, distribution, metabolism, and elimination in healthy adults also determine absorption, distribution, metabolism, and elimination in patients with diabetes mellitus. The extrapolation of the finding of PD similarity of MYL-1501D and U.S.-Lantus in healthy adults to adult patients with T1DM, pediatric patients with T1DM and adult patients with T2DM is justified because the assessed PD endpoints evince the binding and activation of insulin receptors, which is the pertinent MOA for all conditions of use of U.S. Lantus (to the extent known). No comparison of any other scientific factors across the conditions of use were necessary to justify the extrapolation. The extrapolation does not require specific knowledge about the relationship between the PK and PD profiles observed in healthy adults and the PK and PD profiles that would be observed in patients with diabetes mellitus. The data and information in the application, including comparative pharmacokinetic and pharmacodynamic data demonstrating no meaningful differences in time-concentration profile and time-action profile over the duration of action of each product, from Studies 1003 and 1004, supports licensure for the conditions of use for which U.S.-Lantus has been previously approved and for which the applicant is seeking licensure.

The information submitted by the applicant demonstrates that MYL-1501D is biosimilar to and interchangeable with U.S.-Lantus for the following indication (including all of the indicated patient populations) for which the Applicant is seeking licensure and for which U.S.-Lantus has been previously approved:  to improve glycemic control in adults and pediatric patients with T1DM and in adults with T2DM.

**Authors:**
Ann Miller

Patrick Archdeacon

# 7. Labeling Recommendations

## 7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, insulin glargine-yfgn, was found to be conditionally accepted by the Agency (DMEPA review dated January 15, 2021).

## 7.2. Proprietary Name

The proposed proprietary name for MYL-1501D is conditionally approved as SEMGLEE. This name has been reviewed by DMEPA who concluded the name was acceptable (DMEPA review dated October 21, 2020).

DMEPA identified preliminary concerns with the Applicant's proposed proprietary name. The proposed proprietary name for the Applicant's proposed 351(k) interchangeable biosimilar with U.S.-Lantus is SEMGLEE, which is the same proprietary name as the Applicant's currently approved 351(a) insulin glargine under BLA 210605. DMEPA voiced their concerns to the Applicant in a teleconference meeting held September 22, 2020. Among these concerns was the risk for confusion among healthcare providers and lay users if the Applicant's 351(a) product had the same proprietary name as the 351(k) product.

(b) (4) The Applicant intends to introduce the 351(k) product into commercial distribution upon receipt of licensure and simultaneously exhaust the 351(a) product. (b) (4) DMEPA determined this proposal to be acceptable.

## 7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is consistent with CDER/OND best labeling practices and policies, is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

The Applicant is seeking licensure for the same indications for which U.S.-Lantus is currently approved: to improve glycemic control in adult and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. The proposed MYL-1501D labeling incorporated relevant data and information from U.S.-Lantus labeling, with appropriate modifications.

There are multiple approved 351(a) BLAs that have the proper name insulin glargine. Consistent with the Guidance for Industry, Labeling for Biosimilar Products and Draft Guidance for Industry, Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act, and the interchangeability statement in the HIGHLIGHTS section of the prescribing information, references to “insulin glargine” in the labeling for MYL-1501D are to U.S.-Lantus.

**Authors:**

Ann Miller, MD
Clinical Reviewer

Patrick Archdeacon, MD
Clinical Team Leader/CDTL

## 8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 13 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

**Authors:**

Ann Miller, MD
Clinical Reviewer

Patrick Archdeacon, MD
Clinical Team Leader/CDTL

## 9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

**Author:**

Patrick Archdeacon, MD
Clinical Team Leader/CDTL

## 10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA.[15]

The recommendation for this 351(k) BLA seeking licensure of MYL-1501D as interchangeable with U.S.-Lantus is approval. None of these criteria apply to this 351(k) BLA and the Applicant will be exempt from this requirement.

**Authors:**

Ann Miller, MD
Clinical Reviewer

Patrick Archdeacon, MD
Clinical Team Leader/CDTL

## 11. REMS and Postmarketing Requirements and Commitments

### 11.1. Recommendations for Risk Evaluation and Mitigation Strategies

None

### 11.2. Recommendations for Postmarket Requirements and Commitments

None

**Authors:**

Ann Miller
Clinical Reviewer

Patrick Archdeacon
Clincal Team Leader/CDTL

## 12. Division Director Comments

[15] The Pediatric Review Committee (PeRC) meeting was held on March 30, 2021 to review the Applicant's PSP (meeting minutes finalized April 9, 2021). The PeRC agreed that no further pediatric studies would be required.

## 12.1. Division Director (OND – Clinical) Comments

In addition to my role as Associate Director for Therapeutics, I also served as the cross discipline team leader for the review of this application. Consequently, my views are reflected in the preceding review.

**Author:**
Patrick Archdeacon
Associate Director for Therapeutics, DDLO

# 13. Appendices

## 13.1. References

References are listed as footnotes throughout the document.

## 13.2. Financial Disclosure

*Author: Ann Miller*

**Covered Clinical Study: MYL-1501D-1003, MYL-1501D-1004, and MYL-1501D-3003**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: Study MYL-1501D-1003: 4; Study MYL-1501D-1004: 25; Study MYL-1501D-3003: 93 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: n/a<br>Significant payments of other sorts: n/a<br>Proprietary interest in the product tested held by investigator: n/a<br>Significant equity interest held by investigator in Sponsor of covered study: n/a | | |
| Is an attachment provided with | Yes ☐ | No ☐ (Request details from |

| | | |
|---|---|---|
| details of the disclosable financial interests/arrangements: | | Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

The Applicant provided financial disclosure information on all investigators who participated in the 8 clinical studies listed in Table 3. One completed Financial Certification and Disclosure Form 3454 was submitted for all clinical studies. All clinical investigators involved in all the studies have certified to the absence of significant proprietary and/or equity interests, as required by 21 CFR 54.2(b).

## 13.3. Nonclinical Appendices

*Author: Patricia Brundage, PhD*

### 13.3.1. Nonclinical Pharmacology

In vitro studies comparing MYL-1501D to U.S.-Lantus evaluated insulin receptor short and long form (insulin receptor-A [IR-A] and insulin receptor-B [IR-B], respectively) and insulin-like growth factor-1 (IGF-1) receptor binding kinetics, insulin receptor activation (via IR-A and IR-B phosphorylation), metabolic activity (via insulin-stimulated glucose uptake, inhibition of lipolysis, and adipogenesis), and mitogenic activity (via insulin receptor- and IGF-1 receptor-dependent mitogenicity) to demonstrate biosimilarity of the two insulin analog products. The E.U.-approved Lantus was included in the in vitro studies as a comparator; however, as these data were not considered necessary to support a demonstration of biosimilarity or interchangeability, a scientific bridge to justify the use of a non-U.S.-licensed comparator was not required.

On April 23, 2021, the Applicant submitted an amended study report for Study BDL/TR/ BR.15.0003/16/002 as a result of calculation and analysis changes for the total insulin receptor (IR) phosphorylation assay and the IR-B phosphorylation assay; there were no changes to the raw/source data. For the total IR phosphorylation assay, only two independent runs were averaged for one MYL-1501D batch (BS15005866), although three were performed. This changed the average relative potency from 0.95 to 1.00 and the percent coefficient of variation (%CV) from 2.88% to 8.94%. For the IR-B phosphorylation assay, analysts used the Maximum Range, not the Best Range as per the current effective standard test procedure, for the calculation of the average relative potencies for MYL-1501D and U.S.-Lantus. This involved minor changes to the average relative potency and %CV values for MYL-1501D and U.S.-Lantus. Overall, the changes for Study BDL/TR/ BR.15.0003/16/002 were considered to be minor and do not impact the conclusions. The changes are incorporated into the summaries of the study below.

### Insulin Receptor A Binding Kinetics

The binding kinetics of the MYL-1501D (13 batches) to the insulin receptor-A (IR-A) are similar to those of U.S.-Lantus (13 batches). Binding kinetics were assessed using Surface Plasmon Resonance after different concentrations of the MYL-1501D (Process V and VI), U.S.-Lantus, or an insulin reference standard were flowed over a CM5 chip with immobilized IR A.

**IR-A Binding Kinetics of MYL-1501D and U.S.-Lantus**

| | Mean ka (1/Ms) | Mean kd (1/s) | Mean KD (M) |
|---|---|---|---|
| MYL-1501D | 1.438E+6 | 0.031 | 2.167E-8 |
| U.S.-Lantus | 1.427E+6 | 0.029 | 2.030E-8 |

Abbreviations: KD, equilibrium dissociation constant; ka, association rate constant; kd, dissociation rate constant; SD, standard deviation

### Insulin Receptor B Binding Kinetics

The binding kinetics of MYL-1501D (13 batches) to the insulin receptor-B (IR-B) are similar to those of U.S.-Lantus (13 batches). Binding kinetics were assessed using Surface Plasmon Resonance after different concentrations of the MYL-1501D (Process V and VI), U.S.-Lantus, or an insulin reference standard were flowed over a CM5 chip with immobilized IR-B.

**IR-B Binding Kinetics of MYL-1501D and U.S.-Lantus**

| | Mean ka (1/Ms) | Mean kd (1/s) | Mean KD (M) |
|---|---|---|---|
| MYL-1501D | 6.811E+5 | 0.013 | 1.938E-8 |
| U.S.-Lantus | 6.777E+5 | 0.013 | 2.017E-8 |

Abbreviations: KD, equilibrium dissociation constant; ka, association rate constant; kd, dissociation rate constant; SD, standard deviation

### IGF-1 Receptor Binding Kinetics

The binding kinetics of the MYL-1501D (10 batches) to the insulin-like growth factor-1 (IGF-1) receptor are similar to those of U.S.-Lantus (10 batches). Binding kinetics were assessed using Surface Plasmon Resonance after different concentrations of the MYL-1501D, U.S.-Lantus, or an insulin reference standard were flowed over a CM5 chip with immobilized IGF-1 receptor.

**Binding Kinetics of MYL-1501D and U.S.-Lantus**

| | Mean ka (1/Ms) | Mean kd (1/s) | Mean KD (uM) |
|---|---|---|---|
| MYL-1501D | 1.61E+5 | 0.04816 | 0.30 |
| U.S.-Lantus | 1.68E+5 | 0.05042 | 0.30 |

Abbreviations: KD, equilibrium dissociation constant; ka, association rate constant; kd, dissociation rate constant; SD, standard deviation

**Total IR, IR-A, and IR-B Phosphorylation**

The capacity of the MYL-1501D (10 batches) to activate downstream cellular signaling through IR-A and IR-B, as demonstrated by IR-A and IR-B phosphorylation and total insulin receptor (IR) phosphorylation, is similar to that of U.S.-Lantus (10 batches).

Using the AlphaScreen® SureFire® assay, IR-A and IR-B phosphorylation in cellular lysates from CHO-K1 cells engineered to over express either IR-A or IR-B were quantified following treatment with different concentrations of MYL-1501D (Process V and VI), U.S.-Lantus, or an insulin working standard. Total IR phosphorylation induced by MYL-1501D (Process V and VI), U.S.-Lantus, or an insulin working standard was measured in lysates from treated hepatocellular carcinoma (HepG2) cells using the same assay.

**IR-A Phosphorylation in Response to MYL-1501D and U.S.-Lantus**

| | Mean Relative Potency | Range |
|---|---|---|
| MYL-1501D | 1.06 | 0.95 to 1.19 |
| U.S.-Lantus | 1.05 | 0.97 to 1.13 |

**IR-B Phosphorylation in Response to MYL-1501D and U.S.-Lantus**

| | Mean Relative Potency | Range |
|---|---|---|
| MYL-1501D | 1.11 | 0.98 to 1.19 |
| U.S.-Lantus | 1.07 | 0.92 to 1.17 |

**Total IR Phosphorylation in Response to MYL-1501D and U.S.-Lantus**

| | Mean Relative Potency | Range |
|---|---|---|
| MYL-1501D | 1.04 | 0.91 to 1.14 |
| U.S.-Lantus | 1.03 | 0.86 to 1.18 |

**Metabolic Assays: Glucose Uptake**

The metabolic activity, as measured by glucose uptake, of MYL-1501D (8 batches) is similar to that of U.S.-Lantus (8 batches). Glucose uptake by differentiated mouse 3T3-L1 cells treated with different concentrations of MYL-1501D (Process V and VI), U.S.-Lantus, or an insulin working standard was quantified using a glucose oxidase peroxidase reagent and measured via a spectrophotometer.

**Glucose Uptake (Metabolic Potency) in Response to MYL-1501D and U.S.-Lantus**

| | Mean Relative Potency | Range |
|---|---|---|

| | | |
|---|---|---|
| MYL-1501D | 0.97 | 0.90 to 1.06 |
| U.S.-Lantus | 1.04 | 0.94 to 1.12 |

**Metabolic Assays: Adipogenesis**

The metabolic activity, as measured by insulin-stimulated adipogenesis, of MYL-1501D (8 batches) is similar to that of U.S.-Lantus ® (8 batches). Insulin stimulated adipogenesis in differentiated mouse 3T3-L1 cells treated with different concentrations of MYL-1501D (Process V and VI), U.S.-Lantus, or an insulin working standard was assessed using a triglyceride estimation kit to measure free triglycerides.

**Adipogenesis (Metabolic Potency) in Response to MYL-1501D and U.S.-Lantus**

| | Mean Relative Potency | Range |
|---|---|---|
| MYL-1501D | 0.97 | 0.71 to 1.10 |
| U.S.-Lantus | 1.12 | 0.89 to 1.80 |

**Metabolic Assays: Inhibition of Stimulated Lipolysis**

The metabolic activity, as measured by insulin-stimulated inhibition of lipolysis, of MYL-1501D (8 batches) is similar to that of U.S.-Lantus (8 batches). Insulin-stimulated inhibition of lipolysis in differentiated mouse 3T3-L1 cells treated with different concentrations of MYL-1501D (Process V and VI), U.S.-Lantus, or an insulin working standard was assessed using a free fatty acid assay following stimulation with isoproterenol.

**Inhibition of Stimulated Lipolysis (Metabolic Potency) in Response to MYL-1501D and U.S.-Lantus**

| | Mean Relative Potency | Range |
|---|---|---|
| MYL-1501D | 1.047 | 0.749 to 1.350 |
| U.S.-Lantus | 0.932 | 0.574 to 1.550 |

**Mitogenicity Assays**

The IGF-1 receptor-dependent mitogenic activity of MYL-1501D (8 batches) in Saos2 osteosarcoma cells is considered similar to that of U.S.-Lantus (16 batches). The ability to promote the proliferation of Saos2 cells, a human osteosarcoma cell line expressing IGF-1 receptor, was evaluated following treatment with different concentrations of MYL-1501D (Process V and VI), U.S.-Lantus, or an insulin working standard using the redox dye Alamar Blue to assess relative fluorescence.

Additionally, MYL-1501D (3 batches) and U.S.-Lantus (3 batches) exhibit comparable IR-dependent mitogenic activity in H4IIE cells expressing IR-A. The ability of promote the proliferation of H4IIE cells, a rat hepatoma cell line overexpressing IR-A, was

evaluated following treatment with different concentrations of MYL-1501D, U.S.-Lantus, or an insulin working standard using the MTS Cell Viability colorimetric assay.

**Mitogenic Potency of MYL-1501D and U.S.-Lantus in Saos2 IGF-1 Receptor Expressing Cells**

| | Mean Relative Potency | Range |
|---|---|---|
| MYL-1501D | 1.01 | 0.88 to 1.12 |
| U.S.-Lantus | 1.03 | 0.92 to 1.18 |

**Mitogenic Potency of MYL-1501D and U.S.-Lantus in H4IIE IR-A Expressing Cells**

| | Mean Relative Potency | Range |
|---|---|---|
| MYL-1501D | 1.10 | 1.07 to 1.12 |
| U.S.-Lantus | 1.08 | 0.99 to 1.20 |

## 13.4. Clinical Pharmacology Appendices

*Author: Lin Zhou, Manoj Khurana*

### 13.4.1. Summary of Bioanalytical Method Validation and Performance

**Pharmacokinetics**

a. PK assay for MYL-1501D-1003

The plasma concentrations of MYL-1501D and U.S.-Lantus and their metabolites (M1 and M2) were appropriately quantified using a validated LC-MS/MS (GIA3HPP) in Study MYL-1501D-1003.

Both the method validation entitled "*Validation of an Analytical Procedure for the Determination of Glargine and Two Metabolites (Glargine M1 and Glargine M2) in Human Plasma (Normal Healthy and Type 1 Diabetic) using Immunoaffinity Extraction followed by Liquid Chromatography with Tandem Mass Spectrometric Detection (LC MS/MS)-Report 8389482*" and sample analysis for the study (Report 8376861) were performed at (b) (4) More details are assay validation and performance of the assay in Study MYL-1501D-1003 are listed in **Table 15**.

**Table 15. Summary method performance of an LC-MS/MS method to measure study drug and two metabolites (M1 and M2) in human plasma in Study MYL-1501D-1003**

| | | |
|---|---|---|
| **Bioanalytical Method Validation Report Name and Amendments** | ***"Validation of an Analytical Procedure for the Determination of Glargine and Two Metabolites (Glargine M1 and Glargine M2) in Human Plasma (Normal Healthy and Type 1 Diabetic) using Immunoaffinity Extraction followed by Liquid Chromatography with Tandem Mass Spectrometric Detection (LC MS/MS) – Report 8389482"*** | |
| **Method Description** | Study drug, M1, and M2 are quantitatively measured from human $K_2$EDTA plasma using immunoaffinity extraction followed by LC-MS/MS. | |
| **Materials Used for Standard Calibration Curve and Concentration** | MYL-1501D, M1, and M2 in $K_2$EDTA plasma at the following concentrations: 0.1, 0.18, 0.35, 0.6, 0.9, 1.35 and 1.5 ng/mL. | |
| **Validated Assay Range** | 0.1 to 1.5 ng/mL for all analytes | |
| **Material Used for Quality Controls (QCs) and Concentration** | $K_2$EDTA plasma spiked with MYL-1501D, M1, and M2<br>LLQC 100 pg/mL<br>Low QC 250 pg/mL<br>Mid QC 500 pg/mL<br>High QC 1200 pg/mL<br>Dilution QC 5000 pg/mL | |
| **Minimum Required Dilutions (MRDs)** | Not Applicable | |
| **Source and Lot of Reagents** | Not Applicable | |
| **Regression Model and Weighting** | Linear, 1/x | |
| **Validation Parameters** | **Method Validation Summary** | |
| **Standard Calibration Curve Performance During Accuracy and Precision Runs*** | Number of standard calibrators from LLOQ to ULOQ (MYL-1501D, M1, and M2) | 7 |
| | Cumulative Accuracy (% bias) from LLOQ to ULOQ<br>Calibrators for:<br>MYL-1501D<br>M1<br>M2 | <br><br><br>-4.5 to 2.7 %<br>-0.6 to 0.7 %<br>-1.6 to 5.3 % |
| | Cumulative Precision (% CV) from LLOQ to ULOQ<br>Calibrators for:<br>MYL-1501D<br>M1<br>M2 | <br><br><br>≤ 6.2 %<br>≤ 8.6 %<br>≤ 10.1 % |

| | | |
|---|---|---|
| **Performance of QCs During Accuracy and Precision Runs** | **Cumulative Accuracy (% bias) in 4 QCs**<br>QCs for<br>MYL-1501D<br>M1<br>M2 | <br><br>-4.0 to -2.8 %<br>-2.2 to 4.0 %<br>-5.8 to 7.0 % |
| | **Inter-batch % CV**<br>QCs for<br>MYL-1501D<br>M1<br>M2 | <br><br>≤ 7.5 %<br>≤ 10.3 %<br>≤ 12.3 % |
| | **Total Error (TE)**<br>QCs for<br>MYL-1501D<br>M1<br>M2 | <br><br>≤ 4.7 %<br>≤ 14.3 %<br>≤ 19.3 % |
| **Selectivity and Matrix Effect** | Blank Matrix:<br>Blank matrix from a minimum of six different individuals, each from normal healthy and T1DM, analysed without internal standard. Individual matrices (normal healthy and T1DM) tested should demonstrate lack of significant interference (>20.0% of the mean LLOQ calibration standard response and >5.0% of ISTD response in the control zero sample) in the chromatographic regions of the analyte and ISTD.<br><br>Blank matrix results from 24 normal healthy sources fulfilled the acceptance criteria (MYL-1501D, M1, and M2). Blank matrix results from 5 out of 7 T1DM sources fulfilled the acceptance criteria.<br><br>Spiked Matrix:<br>Blank matrix from six different individuals (normal healthy and T1DM), each spiked at the LLOQ QC concentration analysed with internal standard. At least five individual matrices (normal healthy and T1DM) must generate individual concentrations (mean for each matrix sample with more than one replicate) values within ±20.0% bias of the nominal concentration. The mean concentration for the matrices (normal healthy and T1DM) must generate overall mean bias and precision values of ±20.0% from nominal and %RSD ≤20.0% respectively.<br><br>Individual concentration data for 20 out of 24 (>80%) spiked normal healthy sources met acceptance criteria | |

| | |
|---|---|
| | (MYL-1501D, M1, and M2). Mean data for the 24 spiked normal healthy individual blank matrix samples were within the acceptance criteria (MYL-1501D, M1, and M2).<br><br>All 7 spiked T1DM blank matrix samples met the individual and mean acceptance criteria (MYL-1501D, M1, and M2). |
| | Matrix Factor (MF):<br>Blank matrix samples were extracted from six normal healthy individual lots, two individual haemolysed lots and two individual lipemic lots. The %RSD of the individual ISTD normalized MF values must be ≤ 15.0%<br><br>The criteria were fulfilled for each analyte with the following ISTD normalized MF values<br>• MYL-1501D: 2.3 % (LQC); 2.6 % (HQC)<br>• M1: 4.1 % (LQC); 7.8 % (HQC)<br>• M2: 4.3 % (LQC); 3.1 % (HQC) |
| **Interference** | No chromatographic interference was observed at the retention time the analytes and internal standards, and no interference with MYL-1501D, M1, or M2 quantitation was observed at the Low QC level from the following:<br>• Actrapid (2.5 ng/mL)<br>• Glulisine (0.5 ng/mL)<br>• Insulin Lispro (5.0 ng/mL) |
| **Hemolysis Effect** | No effect from hemolysis (2% hemolyzed matrix) on the quantitation of MYL-1501D, M1, or M2 was observed at the LQC and HQC levels. |
| **Lipemic Effect** | No effect from lipemia (≤ 200 mg/mL triglyceride) on the quantitation of MYL-1501D, M1, or M2 was observed at the LQC and HQC levels. |
| **Dilution Linearity** | Highest Concentration Tested: 5.0 ng/mL, M1, and M2<br>Number of Dilution Factors: 1 at 1:10<br>Observed Mean Bias (n=6): Glargine -3.0%, M1 -0.2%, M2 -4.0% |
| **Hook Effect** | Not Applicable |
| **Bench-top/Process Stability** | Stability in fresh vacutainer drawn normal human $K_2$EDTA plasma was demonstrated on wet ice at follows:<br>• MYL-1501D: 6 hours<br>• M1: 12 hours<br>• M2: 12 hours<br><br>Stability of processed samples was demonstrated for 94 hours stored at nominal 5°C for MYL-1501D, M1 and M2. |
| **Freeze-Thaw Stability** | Stability of MYL-1501D, M1, and M2 in fresh vacutainer drawn normal human $K_2$EDTA plasma was demonstrated |

| | |
|---|---|
| | for 3 cycles when stored at -20°C and -80°C and thawed on wet ice. |
| **Long-Term Storage** | Stability in normal human $K_2$EDTA plasma was demonstrated for 392 days when stored at -80°C for MYL-1501D, M1, and M2.<br><br>Stability in human $K_2$EDTA plasma from T1DM patients was demonstrated for 164 days when stored at -20°C and 342 days when stored at -80°C for MYL-1501D, M1, and M2. |
| **Parallelism** | Not Applicable |
| **Carry Over** | Detector response at the analyte and internal standard retention times for the carry-over blank (injected after the ULOQ calibrator) must be ≤ 20% of the response of the analyte and ≤ 5% of the internal standard response, respectively, of the lowest acceptable LLOQ calibrator (analyte) in the run.<br><br>There was no evidence of carryover within the chromatographic regions of the analyte and the ISTD. |

| **Method Performance in Study MYL-1501D-1003<br>Report 8376861 provided in Section 5.3.1.4** | |
|---|---|
| **Validation Parameters** | **Method Validation Summary** |
| **Assay Passing Rate** | A total of 89 sample analysis batches were performed with 8 failing to meet the assay criteria resulting in a 91.0% passing rate |
| **Standard Curve Performance** | • Cumulative bias range (MYL-1501D): -1.7 to 2.0 %<br>• Cumulative precision (MYL-1501D): ≤ 5.2 % CV<br>• Cumulative bias range (M1): -1.4 to 1.0 %<br>• Cumulative precision (M1): ≤ 6.9 % CV<br>• Cumulative bias range (M2): -0.8 to 0.5 %<br>• Cumulative precision (M2): ≤ 8.2 % CV |
| **QC Performance** | • Cumulative bias range (MYL-1501D): 0.0 to 1.6 %<br>• Cumulative precision (MYL-1501D): ≤ 4.3 % CV<br>• Cumulative bias range (M1): -2.5 to -0.8 %<br>• Cumulative precision (M1): ≤ 6.7 % CV<br>• Cumulative bias range (M2): 0.0 to 2.0 %<br>• Cumulative precision (M2): ≤ 7.9 % CV |
| **Method Reproducibility** | Incurred sample re-analysis was performed on 412 study samples (6.0%), and 96.8 % of the samples met the pre-specified criteria (M1) |

| | |
|---|---|
| **Study Sample Analysis/Stability** | Maximum duration of sample storage (first collection date to last extraction date): 317 days<br><br>Validated Long-Term Stability Duration: 392 days |

Source: Adapted from Table 2C of Module 2.7.1 of BLA 761201

b. PK assay for MYL-1501D-1004

The plasma concentrations of MYL-1501D and U.S.-Lantus and their metabolites (M1 and M2) were appropriately quantified using a validated LC-MS/MS (GIA3HPP) in Study MYL-1501D-1004.

Both the method validation entitled "*Validation of an Analytical Procedure for the Determination of Glargine and Two Metabolites (Glargine M1 and Glargine M2) in Human Plasma using Solid Phase Extraction followed by Liquid Chromatography with Tandem Mass Spectrometric Detection (LC MS/MS) – Report 8372478*" and sample analysis (Report 8376860) for the study were performed at (b) (4) . More details are assay validation and performance of the assay in Study MYL-1501D-1003 are listed in **Error! Reference source not found.**.

**Table 16. Summary method performance of an LC-MS/MS method to measure study drug and two metabolites (M1 and M2) in human plasma in Study MYL-1501D-1004**

| | |
|---|---|
| **Bioanalytical Method Validation Report Name and Amendments** | **"*Validation of an Analytical Procedure for the Determination of Glargine and Two Metabolites (Glargine M1 and Glargine M2) in Human Plasma using Solid Phase Extraction followed by Liquid Chromatography with Tandem Mass Spectrometric Detection (LC MS/MS) – Report 8372478*"** |
| **Method Description** | Study drug, M1, and M2 are quantitatively measured from human $K_2$EDTA plasma using solid phase extraction followed by LC-MS/MS. |
| **Materials Used for Standard Calibration Curve and Concentration** | MYL-1501D, M1, and M2 in $K_2$EDTA plasma at the following concentrations: 0.2, 0.3, 0.5, 0.9, 1.5, 2.7 and 3.0 ng/mL |
| **Validated Assay Range** | 0.2 to 3.0 ng/mL for all analytes |
| **Material Used for Quality Controls (QCs) and Concentration** | $K_2$EDTA plasma spiked with MYL-1501D, M1, and M2<br>LLOQ-QC 0.200 ng/mL<br>Low QC (Additional) 0.300 ng/mL<br>Low QC 0.600 ng/mL<br>Middle QC 1.20 ng/mL<br>High QC 2.40 ng/mL<br>Dilution QC 10.0 ng/mL |

| | | |
|---|---|---|
| **Minimum Required Dilutions (MRDs)** | Not Applicable | |
| **Source and Lot of Reagents** | Not Applicable | |
| **Regression Model and Weighting** | Linear, 1/x | |
| **Validation Parameters** | **Method Validation Summary** | |
| **Standard Calibration Curve Performance During Accuracy and Precision Runs*** | Number of standard calibrators from LLOQ to ULOQ (MYL-1501D, M1, M2) | 7 |
| | Cumulative Accuracy (% bias) from LLOQ to ULOQ Calibrators for:<br>MYL-1501D<br>M1<br>M2 | <br><br><br>-1.7 to 1.5 %<br>-0.6 to 2.3 %<br>-3.0 to 2.5 % |
| | Cumulative Precision (% CV) from LLOQ to ULOQ Calibrators for:<br>MYL-1501D<br>M1<br>M2 | <br><br><br>≤ 6.1 %<br>≤ 6.2 %<br>≤ 6.0 % |
| **Performance of QCs During Accuracy and Precision Runs** | **<u>Cumulative Accuracy (% bias) in 5 QCs</u>**<br>QCs for<br>MYL-1501D<br>M1<br>M2 | <br><br>-0.8 to 2.5%<br>-2.5 to 0.0%<br>-3.2 to 3.0% |
| | **<u>Inter-batch % CV</u>**<br>QCs for<br>MYL-1501D<br>M1<br>M2 | <br><br>≤ 6.4 %<br>≤ 9.5 %<br>≤ 7.1 % |
| | **<u>Total Error (TE)</u>**<br>QCs for<br>MYL-1501D<br>M1<br>M2 | <br><br>≤ 8.8 %<br>≤ 12.0 %<br>≤ 13.2 % |
| **Selectivity and Matrix Effect** | <u>Blank Matrix</u>:<br>Blank matrix from a minimum of six different individuals, each from normal healthy and T1DM, analysed without internal standard. Individual matrices (normal healthy and T1DM) tested should demonstrate | |

| | |
|---|---|
| | lack of significant interference (>20.0% of the mean LLOQ calibration standard response and >5.0% of ISTD response in the control zero sample) in the chromatographic regions of the analyte and ISTD.<br><br>Blank matrix results from all normal healthy $K_2$EDTA plasma sources fulfilled the acceptance criteria (MYL-1501D, M1, and M2).<br><br><u>Spiked Matrix</u>:<br>Blank matrix from six different individuals (normal healthy and T1DM), each spiked at the LLOQ QC concentration analysed with internal standard. At least five individual matrices (normal healthy and T1DM) must generate individual concentrations (mean for each matrix sample with more than one replicate) values within ±20.0% bias of the nominal concentration. The mean concentration for the matrices (normal healthy and T1DM) must generate overall mean bias and precision values of ±20.0% from nominal and %RSD ≤20.0% respectively.<br><br>Individual and mean concentration data for the 6 spiked normal healthy $K_2$EDTA plasma sources met acceptance criteria (MYL-1501D, M1, and M2).<br><br>Individual and mean concentration data for the 6 spiked T1DM $K_2$EDTA plasma sources did not meet acceptance criteria (MYL-1501D, M1, and M2). |
| | <u>Matrix Factor (MF)</u>:<br>Blank matrix samples were extracted from six normal healthy individual lots, two individual haemolysed lots and two individual lipemic lots. The %RSD of the individual ISTD normalized MF values must be ≤ 15.0%<br><br>The criteria were fulfilled for each analyte with the following ISTD normalized MF values<br>• MYL-1501D: 1.9 % (LQC); 1.2 % (HQC)<br>• M1: 3.3 % (LQC); 2.2 % (HQC)<br>• M2: 3.4 % (LQC); 2.3 % (HQC) |
| **Interference** | No significant chromatographic interference was observed at the retention time of the analytes or internal standards, and no interference with MYL- |

| | |
|---|---|
| | 1501D, M1, or M2 quantitation was observed at the Low QC level from the following:<br>• Actrapid (2.5 ng/mL) |
| **Hemolysis Effect** | No effect from hemolysis on the quantitation of MYL-1501D, M1, or M2 was observed at the LQC and HQC levels. |
| **Lipemic Effect** | No effect from lipemia on the quantitation of MYL-1501D, M1, or M2 was observed at the LQC and HQC levels. |
| **Dilution Linearity** | Highest Concentration Tested: 10.0 ng/mL MYL-1501D, M1, and M2<br>Number of Dilution Factors: 1 at 1:10<br>Observed Mean Bias: Glargine 3.0%, M1 0.0%, and M2 3.0%. |
| **Hook Effect** | Not Applicable |
| **Bench-top/Process Stability** | Stability in normal human $K_2$EDTA plasma was demonstrated at room temperature (18 hours) and in wet ice (18 hours) for MYL-1501D, M1, and M2.<br><br>Stability of processed samples was demonstrated for 216 hours at 5°C for MYL-1501D, M1, or M2. |
| **Freeze-Thaw Stability** | Stability in normal human $K_2$EDTA plasma was demonstrated for 4 cycles at -20°C and -80°C for MYL-1501D, M1, and M2. |
| **Long-Term Storage** | Stability of MYL-1501D, M1, and M2 in $K_2$EDTA plasma from normal healthy subjects was demonstrated for 538 days and 1416 days when stored at -20°C and -80°C, respectively.<br><br>Stability of MYL-1501D, M1, and M2 in $K_2$EDTA plasma from T1DM patients was demonstrated for 1416 days when stored at -80°C. |
| **Parallelism** | Not Applicable |
| **Carry Over** | The carryover blanks should demonstrate lack of significant interference (>20.0% of the mean (acceptable) LLOQ calibration standard response and >5.0% of ISTD response in the control zero sample) in the chromatographic regions of the analyte and ISTD.<br><br>There was no evidence of carryover within the chromatographic regions of the analytes and internal standards. |
| **Method Performance in Study MYL-1501D-1004 Report 8376860 provided in Section 5.3.1.4** | |

| Validation Parameters | Method Validation Summary |
|---|---|
| **Assay Passing Rate** | A total of 61 sample analysis batches were performed with 4 failing to meet the assay criteria resulting in a 93.4% passing rate |
| **Standard Curve Performance** | • Cumulative bias range (MYL-1501D): -0.4 to 0.3%<br>• Cumulative precision (MYL-1501D): ≤ 6.5% CV<br>• Cumulative bias range (M1): -1.0 to 1.1%<br>• Cumulative precision (M1): ≤ 7.1% CV<br>• Cumulative bias range (M2): -1.0 to 0.6%<br>• Cumulative precision (M2): ≤ 7.4% CV |
| **QC Performance** | • Cumulative bias range (MYL-1501D): -1.0 to 0.8%<br>• Cumulative precision (MYL-1501D): ≤ 5.1% CV<br>• Cumulative bias range (M1): -0.7 to 0.8%<br>• Cumulative precision (M1): ≤ 5.5% CV<br>• Cumulative bias range (M2): 0.8 to 1.7%<br>• Cumulative precision (M2): ≤ 6.7% CV |
| **Method Reproducibility** | Incurred sample re-analysis was performed on 187 study samples (7.2%), and 94.1 % of the samples met the pre-specified criteria (M1) |
| **Study Sample Analysis/Stability** | Maximum duration of sample storage (first collection date to last extraction date): 122 days<br><br>Validated Long-Term Stability Duration: 1416 days |

Source: Adapted from Table 2D of Module 2.7.1 of BLA 761201

**Pharmacodynamics**

**Bioanalytical methods that were used to assess the PD biomarker(s) and/or the PD effect(s) of the study drug(s)**

In both Study MYL-1501D-1003 and Study MYL-1501D-1004, the euglycaemic glucose clamp was performed by means of a glucose clamp device (ClampArt; Profil Neuss, Germany). Subjects were connected to ClampArt which monitored the subject's blood glucose continuously. The device calculated an average blood glucose value every minute. Based on this average value GIRs were calculated every minute using the algorithm implemented into the device and were administered automatically by the device to keep the subject's blood glucose concentration constant at a pre-determined target level. The device's glucose measurements were verified approximately every 30 minutes or more frequently, if needed, by blood glucose measurements with a laboratory glucose analyzer (Super GL glucose analyzer).

The current procedures are in accordance with the US Code of Federal Regulations (see Title 21, Chapter I, Subchapter A, Part 58 Good Laboratory Practice [GLP] for nonclinical laboratory studies) and Federal Register for GLP paragraph 121 ("Proper

standards [for calibration] are the responsibility of the management, and these are to be set forth in the standard operating procedures [SOPs]"). All procedures regarding measurements with and QC of the device are regulated by SOPs.

## 13.5. Clinical Appendices

*Author: Ann Miller*

As previously discussed, the Applicant submitted several clinical studies in support of this 351(k) application. During the course of the review, FDA determined that comparative clinical immunogenicity studies were not necessary to support the 351(k) application. For that reason, these clinical studies were reviewed only to confirm that their results did not preclude nor conflict with conclusions made from other data and information. All of the studies with the exception of MYL-1501D-3003 had been previously submitted and reviewed in the context of NDA 210605. Other than the euglycemic clamp PK/PD studies, the results of those studies (with the exception of MYL-1501D-3004 to support the demonstration of comparability between MYL-1501D Process V and Process VI[16]) were supportive but not necessary to the determination that MYL-1501D is biosimilar to or interchangeable with U.S.-Lantus. Because MYL-1501D-3003 was not necessary to support the demonstration of biosimilarity or interchangeability of MYL-1501D and U.S.-Lantus, its review appears in this appendix rather than in the body of the BMER. The results of MYL-1501D-3003 are supportive but not necessary to the determination that MYL-1501D is biosimilar to or interchangeable with U.S.-Lantus.

### 13.5.1. MYL-1501D-3003

Study MYL-1501D-3003 was a multicenter, open-label, randomized, parallel-group study designed to compare the efficacy and safety of MYL-1501D to U.S.-Lantus in patients with type 1 diabetes.

MYL-1501D-3003 was designed as a switching study to support a demonstration of interchangeability. However, FDA did not consider the study design appropriate for that purpose. The FDA review of study MYL-1501D-3003 was performed with prior knowledge that the design of the study was inadequate to support the regulatory requirements to demonstrate interchangeability. FDA approached this review with the objective of ensuring that there were no data that would preclude a determination of biosimilarity or interchangeability. Therefore, although additional study design limitations surfaced during this study's review, these were considered to be inconsequential, as these design limitations did not interfere with the review's objective.

[16] As noted above, study MYL-1501D-3004, along with additional data and information, supported the demonstration of comparability between Process V and Process VI, as the applicant's analytical data included materials manufactured using both Process V and Process VI.

## Data and Analysis Quality

There are no concerns regarding data quality and integrity of study MYL-1501D-3003. It is important to note that the data were inspected only to ensure that the results of this study would not preclude or conflict with the conclusions of the other studies submitted by the Applicant which the Agency is relying on to support the demonstration of biosimilarity and interchangeability. The data were inspected in a manner consistent with the objective of this review, as these studies were not necessary to demonstrate biosimilarity or interchangeability.

## Study Design and Endpoints

### Study Title

*An Open-label, Randomized, Multi-center, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus in Type 1 Diabetes Mellitus Patients: An Extension Study*

### Study Design

Study MYL-1501D-3003 was designed as an extension study of MYL-GAI-3001. Both studies were multi-center, open-label, randomized, parallel-group studies. Study MYL-GAI-3001 compared the efficacy and safety of MYL-1501D Process V to U.S.-Lantus. The study included male and female patients 18-65 years of age with an established diagnosis of T1DM per the American Diabetes Association 2014 criteria.[17] The patients in the MYL-GAI-3001 study randomized to the U.S.-Lantus arm who completed 52 weeks of treatment were offered the opportunity to participate in study MYL-1501D-3003.

Figure 10 illustrates the MYL-1501D-3003 study design. Eligible and consenting patients from the U.S.-Lantus arm of the MYL-GAI-3001 study were randomized into one of two treatment arms: the switching treatment arm or U.S.-Lantus treatment arm. The week 52 visit in the MYL-GAI-3001 study served as the week 0 visit for study MYL-1501D-3003. The MYL-1501D-3003 study lasted 40 weeks. The patients were treated with their assigned study product for 36 weeks.

The 36 weeks of study product treatment were divided into three treatment Periods. Each Period lasted 12 weeks. Patients in the switching treatment arm received MYL-1501D during Periods 1 and 3. They received U.S.-Lantus during Period 2. The patients in the U.S.-Lantus arm received U.S.-Lantus during all three treatment Periods. After 36 weeks of study product treatment, the patients resumed their baseline diabetes treatment for an additional 4 weeks. Patients underwent a follow up visit after those 4 weeks.

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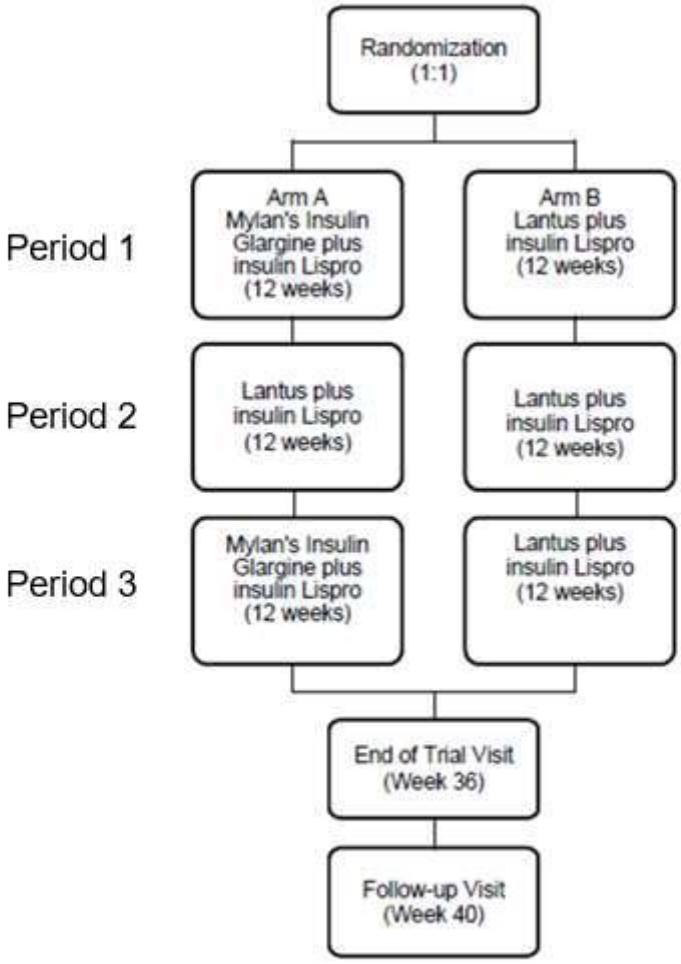
[17] (2014). "Standards of Medical Care in Diabetes—2014." Diabetes Care 37(Supplement 1): S14-S80.

**Figure 10. Schematic of Study Design**




Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, Figure 9-1: Schematic of Study Design

Key Inclusion Criteria

Patients must have met all the inclusion criteria to be considered eligible for the study.

1. Patients met the inclusion criteria for study MYL-GAI-3001, were assigned to the U.S.-Lantus arm, and completed the 52-weeks of treatment. Patients included in study MYL-GAI-3001 were 18 to 65 years of age with a diagnosis of T1DM and met all the following criteria:
    i. Initiation of insulin within 6 months of diagnosis of T1DM
    ii. Treatment with basal-bolus insulin for at least 1 year prior to screening
    iii. Fasting C-peptide < 0.3 nmol/L at screening

iv. Previous treatment with a stable dose of Lantus (± 15% variation in dose) for at least 3 months prior to screening
v. Body mass index (BMI) of 18.5 to 35 kg/$m^2$ at screening, both values inclusive
vi. Glycosylated hemoglobin ≤ 9.5% at screening

2. Patients were able and willing to comply with the requirements of the extension study protocol.
3. Female patients complied with the following:
    a. Female patients of childbearing potential must have been using oral contraception or two other acceptable methods of contraception from the time of randomization throughout the study.
    b. Periodic abstinence and withdrawal were not acceptable methods of contraception.
    c. Postmenopausal females must have had no menstrual bleeding for at least 1 year prior to inclusion in the MYL-1501D-3003 study.
    d. Female patients who reported surgical sterilization must have had the procedure at least 6 months prior to inclusion in the MYL-1501D-3003 study.
4. All female patients of childbearing potential must have had a negative pregnancy test result at baseline (Week 0) and at each clinic visit as per the Schedule of Activities (see **Section 13.5.5**).
5. If a female patient had a male partner, and the male partner had undergone a vasectomy, the vasectomy must have occurred more than 6 months prior to the female patient's inclusion in the MYL-1501D-3003 study.

Key Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

1. The patient had a history or presence of a medical condition or disease that in the Investigator's opinion would have placed the patient at an unacceptable risk for study participation.
2. The patient had a history of clinically significant (i.e., significant enough to alter the insulin dose requirement, as per the Investigator) acute bacterial, viral, or fungal systemic infection in the 4 weeks prior to inclusion/randomization (recorded while collecting patient history) into the MYL-1501D-3003 study.
3. The patient was scheduled to receive another investigational drug during the MYL-1501D-3003 study treatment period.
4. The patient had major elective surgery planned during the study period that would require hospitalization.
5. The patient had moderate insulin resistance (defined as requiring a total daily dose of insulin (basal + prandial) of ≥ 1.5 U/kg/day (U.S.-Lantus in U/kg/day or MYL-1501D in IU/kg/day)).

**Study Treatment**

Patients were treated with either MYL-1501D (100 IU/mL) or U.S.-Lantus (from Sanofi sourced from the US; 100 IU/mL). Importantly, the MYL-1501D study product used was MYL-1501D Process V. U.S.-Lantus served as the study comparator product. Patients administered their assigned study product treatment using a pre-filled disposable pen with a 3 mL cartridge. The cartridge held the study product. Patients also received Humalog (insulin lispro injection, 100 U/mL) (manufactured by Eli Lilly) to be used as mealtime insulin.

An Interactive Web Response System randomized the study patients. The MYL-GAI-3001 randomization number was collected in conjunction with a new randomization number for study MYL-1501D-3003.

The Applicant conducted the study as open-label. U.S.-Lantus and MYL-1501D have different manufacturers and distinct packaging was needed. Thus, the Investigators and patients were not blinded to the treatment assignments. To minimize bias, the Applicant did not reveal treatment assignments to the bioanalytical laboratory for the antibody determinations, the central laboratory for the safety and efficacy analysis, or the study team members who were not in direct contact with the sites during the study duration.

The patients administered their assigned study product treatment as a once daily subcutaneous injection with a dose determined by the Investigator. Although dose titration was kept to a minimum, titration algorithms for both study products and Humalog were provided. The suggested dose titration algorithm for the insulin glargine study products is shown below (Table 17).

**Table 17. Suggested Basal Insulin Dose Titration Algorithm**

| **Lowest Fasting Capillary Blood Glucose (Pre-Breakfast) Value For 3 Days** | **Adjust Basal Insulin Dose (U per dose) (U.S.-Lantus or MYL-1501D)** |
|---|---|
| >270 mg/dL | + 6 U |
| 181-270 mg/dL | + 4 U |
| 151-180 mg/dL | + 2 U |
| 131-150 mg/dL | + 1 U |
| 71-130 mg/dL (Target level) | Maintain Dose |
| 56-70 mg/dL | - 2 U |
| <56 mg/dL | - 4 U |

Source: Adapted from MYL-1501D-3003 Extension Study Protocol Appendix II: Suggested Guidance for Insulin Dose Titration

**Administrative Structure**

A full schedule of activities is outlined in **Section 13.5.5**. Approximately 138 patients were planned to be enrolled in this study.

**Study Endpoints**

The primary clinical endpoint was change in HbA1c from baseline at week 36.

Secondary clinical endpoints:

- HbA1c change from baseline at scheduled visits
- Fasting plasma glucose (FPG) change from baseline at scheduled visits (fasting defined as no intake of food or drink (except water) for at least 10 hours)
- Change in 8-point self-monitored blood glucose (SMBG) levels from baseline at scheduled visits (an 8-point SMBG profile was performed by the patient at home and recorded in a diary for three days in the week preceding the next visit): individual pre-meal, individual post-meal, individual 2-hour excursion after meals, bedtime, overall (average) pre-meal, overall post-meal, overall excursion, 4-point average (pre-meal + bedtime), and daily average
- Change in daily insulin dose/unit body weight for days of 8-point SMBG profile documentation (daily prandial dose, basal insulin dose, total daily dose) from baseline at scheduled visits

Safety endpoints:

- Anti-drug antibodies (ADA) present determined in terms of percent specific binding
- Presence of antibodies directed against host cell proteins (anti-HCP)
- Hypoglycemia rate per patient per 30 days
- Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)

Other safety endpoints included change from baseline in vital signs and laboratory measurements as well as electrocardiogram (ECG) abnormalities and assessment of device safety.

**Dietary restrictions/instructions**

Patients were instructed to follow a recommended diet and exercise plan for the duration of the study, but this was not defined in the study protocol.

**Concurrent medications**

Although not explicitly part of the exclusion criteria, use of insulin products (apart from the study insulin formulations), insulin analogs, and other anti-diabetes medications and glucocorticoid therapies (oral, intravenous, inhaled, or other routes that produce systemic effects) were prohibited during the study (including the run-in period and the comparative phase).

The study protocol also outlined a list of restricted medications, shown in Table 18, that were not allowed to be started during the 36 weeks of study treatment because of possible interference with insulin.

**Table 18. Medications That Are Likely to Interfere with Diabetes Control**

| Drug Classes That Are Known To Augment The Blood Glucose Lowering Effect Of Insulin Such As: | Drugs And Drug Classes That Are Known To Decrease The Blood Glucose Lowering Effect Of Insulin Such As: |
|---|---|
| Salicylates at doses more than > 2g/day<br>Sulfa antibiotics<br>Angiotensin converting enzyme inhibitors<br>Disopyramide<br>Fibrates<br>Fluoxetine<br>Monoamine oxidase inhibitors<br>Propoxyphene<br>Pentoxifylline<br>Somatostatin analogs<br>Bromergocryptine (bromocriptine)<br>Anabolic steroids | Danazol<br>Niacin<br>Diuretics<br>Sympathomimetic agents<br>Glucagon<br>Isoniazid<br>Somatropin<br>Thyroid hormones<br>Oral contraceptives<br>Estrogens<br>Progestogens<br>Protease inhibitors<br>Phenothiazine derivatives<br>Atypical antipsychotic medications (e.g. olanzapine and clozapine) |

Source: Adapted from MYL-1501D-3003 Extension Study Protocol Table 2: Medications That Are Likely to Interfere with Diabetes Control

**Treatment Compliance**

Treatment compliance was assessed at each study visit. The Investigator reviewed the diary with the patient and assessed compliance based on documented results of the 8-point SMBG measurements, insulin doses, and documentation of any AEs, hypoglycemia, or device related issues.

Patients were considered non-compliant if they met any of the following criteria:

- Missing total mealtime insulin or basal insulin doses for 5 consecutive days
- Missing total mealtime insulin or basal insulin doses for more than 30 accumulative days for those who completed the study or more than 20% of treatment days for patients considered dropouts
- Taking more than 1 administration of basal insulin for 10 days total
- Taking more than the prescribed basal insulin dose for more than 30 days total

The patients who were considered non-compliant by the Investigator were withdrawn from the study.

*Reviewer comments:*
*The objective of this study's review was to ensure that there were no data that preclude a determination of biosimilarity or interchangeability. In this context, the primary clinical endpoint of change in HbA1c from baseline at week 36 was relevant. Any significant differences in the primary clinical endpoint between the treatment arms could raise residual uncertainty that may preclude a demonstration of biosimilarity or interchangeability. Other study design features that were relevant to the review's objective included the use of U.S.-Lantus as the comparator product, the study patient inclusion and exclusion criteria, and the safety and secondary clinical endpoints.*

**Statistical Methodologies**

The final analysis was performed by the Quintiles Biostatistics team following the Applicant's authorization of the statistical analysis plan and database lock. The Applicant defined the following populations prior to database lock:

- Randomized population: all patients enrolled and randomized to one of the study products
- Safety population: randomized patients who took at least one dose of the study product
- Intent-to-treat (ITT) population: all randomized patients who had a baseline and at least one post-baseline visit
- Modified intent-to-treat (mITT) population: all randomized patients who had at least one baseline HbA1c value and one post-baseline HbA1c value during treatment Period 3 ($24 < \text{week} \leq 36$)
- Per protocol (PP) population: patients who had at least one baseline and one Period 3 value and did not have protocol violations that impacted the primary outcome. Patients excluded from the PP population were identified prior to the database lock

**Statistical Considerations for Primary Endpoint Analysis**

The primary endpoint analysis was conducted in the mITT population. An analysis of covariance (ANCOVA) was performed on the primary outcome variable. The model included region and treatment arm as fixed effects, and baseline HbA1c as a covariate. The ANCOVA method produced a 95% confidence interval (CI) for the difference between the two treatment arms for mean change in HbA1c at week 36 from baseline. The Applicant defined equivalence to be supported if the 95% CI was within ± 0.4% equivalence limits.

Missing primary efficacy data was not imputed except when the week 36 HbA1c value was missing on account of early discontinuation. In this instance, the Applicant used the exit measurement of or last non-missing value from Period 3 instead. Sensitivity analysis for the primary efficacy variable was performed using the ITT and PP populations.

The Applicant's primary endpoint was too insensitive of an endpoint to serve as the only basis on which to evaluate whether the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. For that reason, the Applicant's definition of equivalence to support the analysis of the endpoint is irrelevant.

**Statistical Considerations for Secondary Endpoint Analyses**

The Applicant performed the secondary efficacy analyses on the ITT population. The Applicant used a repeated measures analysis employing a restricted maximum likelihood (REML)-based, mixed-effects model approach (MMRM) to compare treatment arm differences at scheduled visits. The model included treatment arm, region, visit, treatment arm-by-visit interaction as fixed effects and baseline values as covariates. For patients considered dropouts, if the last post baseline data value did not fall at the scheduled visit, the Applicant mapped it to the next scheduled visit and included it in the analyses. For secondary endpoints considered continuous variables, differences in least square (LS) means at each scheduled visit were used to evaluate all pairwise treatment arm comparisons, and a 95% CI for treatment arm differences in LS means was computed for each visit.

**Safety Outcomes**

The Applicant performed the safety analyses using the safety population. The definitions of adverse event (AE) and treatment emergent adverse event (TEAE) are explained in the review of safety data in **Section 13.5.2**. The safety analyses data were presented by treatment arm for each treatment Period. The Applicant performed treatment arm comparisons using Fisher's exact test for each treatment Period.

**Device safety assessment**

The Applicant assessed device safety using the patient responses to an Investigator-administered device questionnaire and incidences of device-related AEs. The total incidence of device-related safety events was summarized for each treatment arm and included device-related TEAEs and events related to device complaints or failures. The Applicant performed treatment arm comparisons using Fisher's exact test.

**Immunogenicity**

The Applicant analyzed immunogenicity profiles with a continuous variable, such as % binding, using the MMRM method for each assay, similar to the change from baseline efficacy analyses. The model included region, treatment arm, visit, and treatment arm-by-visit as fixed effects, and baseline value as a covariate. The treatment arm difference and 95% CIs were calculated using the model at scheduled visits. The safety population was used in the analyses using ADA continuous variables.

The Applicant summarized immunogenicity profiles with dichotomous outcomes by frequency and percentage at scheduled visits for each assay. The treatment arm comparison was done using Fisher's exact test.

The Applicant also performed correlation analyses of insulin cross-reactive antibodies with clinical factors such as HbA1c and insulin doses by treatment arm to explore the relationship of insulin antibodies with such factors.

The Applicant performed these immunogenicity analyses based on the Agency's recommendations in the October 2018 BPD Type 2 meeting. However, the Agency's recommendations were superseded by the *Insulin Immunogenicity Guidance*. As described above, a comparative clinical immunogenicity study was not necessary to support a demonstration of biosimilarity or interchangeability for MYL-1501D.

Thus, the immunogenicity analyses performed by the Applicant in this study were not required to support the demonstration of interchangeability. However, the Applicant referenced the results of these analyses in the immunogenicity assessment. In keeping with the objective of this study's review, the Applicant's immunogenicity analyses were reviewed to ensure that the data did not preclude a demonstration of biosimilarity or interchangeability.

**Protocol Amendments**

The Applicant amended the original protocol once after the start of the study. The Applicant added treatment Period 3 (weeks 24-36) and changed the primary analysis population from the ITT population to the mITT population. The Applicant also changed the primary endpoint analysis from non-inferiority to equivalence.

Given that the Applicant's primary endpoint was not appropriate as described above, these protocol amendments were irrelevant. However, these protocol amendments did not interfere with the review's objective of ensuring that the data do not preclude a demonstration of biosimilarity or interchangeability.

**Subject Disposition**

Table 3Table 19 illustrates the patient disposition for the randomized population. 127 patients were randomized to either the switching treatment arm (64 patients) or the U.S.-Lantus treatment arm (63 patients). 119 patients completed the study, resulting in a retention rate of 93.7%. Both treatment arms had a retention rate > 90%.

8 patients did not complete the study. Their reasons for study discontinuation are included in the table. The most common reason for study discontinuation was withdrawal of consent. Reasons for withdrawal of consent were not provided by the Applicant, but a majority of the patients who withdrew consent were in the U.S.-Lantus

arm. This is unlikely to affect the data given the overall high retention rate in both treatment arms.

The mITT population used for the primary efficacy analysis included 118 patients, 61 from the switching arm and 57 from the U.S.-Lantus arm. All 118 patients completed the study.

All patients in the randomized population met the criteria for inclusion into the safety population.

**Table 19. Patient Disposition (Randomized Population)**

| Disposition | U.S.-Lantus N = 63 n (%) | Switching arm N = 64 n (%) | Total N = 127 n (%) | P-value |
|---|---|---|---|---|
| Patients completed the study (overall) | 58 (92.1) | 61 (95.3) | 119 (93.7) | |
| Patients discontinued the study (overall) | 5 (7.9) | 3 (4.7) | 8 (6.3) | .492 |
| Reason for study discontinuation (overall) | | | | |
| Withdrawal of consent | 4 (6.3) | 1 (1.6) | 5 (3.9) | |
| Adverse event* | 1 (1.6) | 0 | 1 (0.8) | |
| Lost to follow-up | 0 | 2 (3.1) | 2 (1.6) | |
| Patients completed Week 12 (Period 1) | 62 (98.4) | 63 (98.4) | 125 (98.4) | |
| Patients discontinued before Week 12 (Period 1) | 1 (1.6) | 1 (1.6) | 2 (1.6) | >.999 |
| Reason for study discontinuation before Week 12 (Period 1) | | | | |
| Adverse event* | 1 (1.6) | 0 | 1 (0.8) | |
| Lost to follow-up | 0 | 1 (1.6) | 1 (0.8) | |
| Patients completed Week 24 (Period 2) | 58 (92.1) | 62 (96.9) | 120 (94.5) | |
| Patients discontinued between Week 12 and Week 24 (Period 2) | 4 (6.3) | 1 (1.6) | 5 (3.9) | .207 |
| Reason for study discontinuation between Week 12 and Week 24 (Period 2) | | | | |
| Withdrawal of consent | 4 (6.3) | 1 (1.6) | 5 (3.9) | |
| Patients completed Week 36 (Period 3) | 58 (92.1) | 61 (95.3) | 119 (93.7) | |
| Patients discontinued between Week 24 and Week 36 (Period 3) | 0 | 1 (1.6) | 1 (0.8) | >.999 |
| Reason for study discontinuation between Week 24 and Week 36 (Period 3) | | | | |
| Lost to follow-up | 0 | 1 (1.6) | 1 (0.8) | |

Abbreviations: N = total number of patients in treatment arm; n = number of patients
*Grade 5 injury as a result of a car versus pedestrian motor vehicle accident
Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, Table 10-1; confirmed by clinical reviewer

Table 20 summarizes the proportion of patients with major and minor protocol deviations and the categories of protocol deviations between the treatment arms. Overall, there were no large differences between the rates of major and minor protocol deviations between the two treatment arms. There were no notable differences between the two arms when the protocol deviations were evaluated further by category.

**Table 20. Summary of Patients with Protocol Deviations by Treatment Sequence (Randomized Population)**

| Deviation (overall) | U.S.-Lantus N = 63 n (%) | Switching arm N = 64 n (%) | Total N = 127 n (%) | P-value |
|---|---|---|---|---|
| **Patients with major protocol deviations** | **16 (25.0)** | **15 (23.8)** | **31 (24.4)** | **.876** |
| Administrative criteria | 0 | 1 (1.6) | 1 (0.8) | |
| Concomitant medication criteria | 1 (1.6) | 1 (1.6) | 2 (1.6) | |
| IP compliance | 5 (7.8) | 2 (3.2) | 7 (5.5) | |
| Informed consent | 5 (7.8) | 6 (9.5) | 11 (8.7) | |
| Serious adverse event criteria | 1 (1.6) | 0 | 1 (0.8) | |
| Study procedures criteria | 2 (3.1) | 2 (3.2) | 4 (3.1) | |
| Visit schedule criteria | 2 (3.1) | 5 (7.9) | 7 (5.5) | |
| | | | | |
| **Patients with minor protocol deviations** | **44 (68.8)** | **48 (76.2)** | **92 (72.4)** | **.348** |
| Administrative criteria | 1 (1.6) | 1 (1.6) | 2 (1.6) | |
| Concomitant medication criteria | 7 (10.9) | 7 (11.1) | 14 (11.0) | |
| Eligibility and Entry Criteria | 3 (4.7) | 1 (1.6) | 4 (3.1) | |
| IP compliance | 6 (9.4) | 7 (11.1) | 13 (10.2) | |
| Laboratory assessment | 2 (3.1) | 4 (6.3) | 6 (4.7) | |
| Other criteria | 4 (6.3) | 3 (4.8) | 7 (5.5) | |

Abbreviations: N = total number of patients in treatment sequence; n = number of patients; IP = investigational product
Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, Table 10-2

## Demographics and Baseline Characteristics

Table 21 summarizes the baseline demographics of the randomized population. About half of the study population was from the United States. Treatment arms were balanced in terms of sex, age, race, baseline HbA1c, BMI, and duration of diabetes. Notably, the majority of the patients in the study were Caucasian (94.5%). This finding does not interfere with the review's objective to ensure the data do not preclude a demonstration of biosimilarity or interchangeability.

**Table 21. Demographic characteristics of the randomized population**

| Subgroup | U.S.-Lantus (N = 63) n (%) | Switching arm (N = 64) n (%) | Total (N = 127) n (%) |
|---|---|---|---|
| Sex | | | |
| Female | 27 (42.9) | 23 (35.9) | 50 (39.4) |
| Male | 36 (57.1) | 41 (64.1) | 77 (60.6) |
| Age (years) | | | |
| Mean | 43.2 | 44.8 | 44.0 |
| Standard Deviation | 12.7 | 11.4 | 12.1 |
| Minimum | 20 | 20 | 20 |
| Median | 44 | 44.5 | 44 |
| Maximum | 66 | 66 | 66 |
| Age Group | | | |
| Under 65 (AGE < 65) | 59 (93.7) | 63 (98.4) | 122 (96.1) |
| Over 65 (65 ≤ AGE) | 4 (6.3) | 1 (1.6) | 5 (3.9) |
| Race | | | |
| Asian | 0 (0.0) | 2 (3.1) | 2 (1.6) |
| Black or African American | 2 (3.2) | 2 (3.1) | 4 (3.1) |
| Other | 0 (0.0) | 1 (1.6) | 1 (0.8) |
| White | 61 (96.8) | 59 (92.2) | 120 (94.5) |
| Region | | | |
| Canada | 1 (1.6) | 2 (3.1) | 3 (2.4) |
| Europe | 27 (42.9) | 30 (46.9) | 57 (44.9) |
| United States | 35 (55.6) | 32 (50.0) | 67 (52.8) |
| Baseline HbA1c (%) | | | |
| Mean | 7.9 | 7.6 | 7.8 |
| Standard Deviation | 0.9 | 1 | 1 |
| Minimum | 5.9 | 5 | 5 |
| Median | 7.8 | 7.6 | 7.8 |
| Maximum | 10.1 | 10.5 | 10.5 |
| Baseline Fasting Plasma Glucose (mmol/L) | | | |
| Mean | 9.5 | 9.8 | 9.7 |
| Standard Deviation | 4.1 | 3.5 | 3.8 |
| Minimum | 3.4 | 3.2 | 3.2 |
| Median | 8.3 | 9.4 | 9.1 |
| Maximum | 21.9 | 17.3 | 21.9 |
| Baseline BMI ($kg/m^2$) | | | |
| Mean | 27.1 | 26.7 | 26.9 |
| Standard Deviation | 4.4 | 4.2 | 4.3 |
| Minimum | 18.6 | 19.8 | 18.6 |

| | | | |
|---|---|---|---|
| Median | 26.9 | 26.3 | 26.6 |
| Maximum | 35.7 | 36.8 | 36.8 |
| Baseline Weight (kg) | | | |
| Mean | 82.4 | 80.7 | 81.6 |
| Standard Deviation | 15.3 | 16.5 | 15.9 |
| Minimum | 53.4 | 54.7 | 53.4 |
| Median | 82 | 78.2 | 80 |
| Maximum | 121 | 120.2 | 121 |
| Duration of Diabetes (years) | | | |
| Mean | 20.2 | 21.4 | 20.8 |
| Standard Deviation | 9.0 | 12.9 | 11.1 |
| Minimum | 2.8 | 0 | 0 |
| Median | 19.8 | 20.3 | 20.3 |
| Maximum | 40.0 | 49.5 | 49.5 |

Abbreviations: N = total number of patients in treatment sequence; n = number of patients; HbA1c = glycosylated hemoglobin; BMI = body mass index; kg = kilogram
Source: Table created by Clinical Reviewer using the ADSL dataset; similar to the demographics table in the Clinical Study Report for MYL-1501D-3003

In total, 113 (89%) patients, 57 (90.5%) in the U.S.-Lantus arm and 56 (87.5%) in the switching arm, were taking concomitant medications. The Applicant defined concomitant medications as medications that were started prior to, on, or after the first dose of the randomized study product and ended after the dose of the randomized study product or was ongoing at the end of the study. Medications taken by > 5% of the total study population are shown below in Table 22.

Approximately 25-30% of the patient population was taking an ACE inhibitor or HMG CoA reductase inhibitor. This is expected as these medications are often prescribed to patients with diabetes. There was an imbalance between treatment arms with regard to selective serotonin reuptake inhibitors and extended spectrum penicillins. The former was more prevalent in the U.S.-Lantus arm; the latter was more prevalent in the switching arm. The difference in extended spectrum penicillin use could indicate that the patients in the switching arm experienced more bacterial infections than those in the U.S.-Lantus arm. This could impact the efficacy and safety analyses as infections can cause fluctuations in blood sugar resulting in significant hyper- or hypoglycemia. Otherwise, there were no major differences in concomitant medications between the two treatment arms. These findings are unlikely to significantly affect the study outcome or interfere with the review's objective of ensuring that the data do not preclude a demonstration of biosimilarity or interchangeability.

**Table 22. Concomitant medications taken by study participants (Randomized Population)**

| | U.S.-Lantus (N = 63) | Switching Arm (N = 64) | Total (N = 127) |
|---|---|---|---|
| **Medication Class*** | **n (%)** | **n (%)** | **n (%)** |
| Ace inhibitors, plain | 21 (33.3) | 16 (25.0) | 37 (29.1) |
| HMG CoA reductase inhibitors | 17 (27.0) | 16 (25.0) | 33 (26.0) |
| Platelet aggregation inhibitors excl. heparin | 10 (15.9) | 11 (17.2) | 21 (16.5) |
| Thyroid hormones | 11 (17.5) | 8 (12.5) | 19 (15.0) |
| Propionic acid derivatives | 12 (19.0) | 6 (9.4) | 18 (14.2) |
| Anilides | 6 (9.5) | 8 (12.5) | 14 (11.0) |
| Beta blocking agents, selective | 8 (12.7) | 6 (9.4) | 14 (11.0) |
| Selective serotonin reuptake inhibitors | 10 (15.9) | 2 (3.1) | 12 (9.4) |
| Various alimentary tract and metabolism products | 6 (9.5) | 5 (7.8) | 11 (8.7) |
| Vitamin D and analogues | 7 (11.1) | 4 (6.2) | 11 (8.7) |
| Angiotensin II antagonists, plain | 5 (7.9) | 5 (7.8) | 10 (7.9) |
| Ascorbic acid (Vitamin C), plain | 6 (9.5) | 4 (6.2) | 10 (7.9) |
| Progestogens and estrogens, fixed combinations | 5 (7.9) | 4 (6.2) | 9 (7.1) |
| Dihydropyridine derivatives | 4 (6.3) | 4 (6.2) | 8 (6.3) |
| Other analgesics and antipyretics | 6 (9.5) | 2 (3.1) | 8 (6.3) |
| Proton pump inhibitors | 3 (4.8) | 5 (7.8) | 8 (6.3) |
| Macrolides | 3 (4.8) | 4 (6.2) | 7 (5.5) |
| Multivitamins, plain | 3 (4.8) | 4 (6.2) | 7 (5.5) |
| Other antidepressants | 4 (6.3) | 3 (4.7) | 7 (5.5) |
| Other antihistamines for systemic use | 2 (3.2) | 5 (7.8) | 7 (5.5) |
| Penicillins with extended spectrum | 1 (1.6) | 6 (9.4) | 7 (5.5) |

Abbreviations: N = total number of patients in treatment sequence; n = number of patients
Source: Table generated by Clinical Reviewer using ADSL and ADCM datasets
*Anatomical Therapeutic Chemical level 4 classification

**Analysis of Primary Clinical Endpoint(s)**

The Applicant's calculation of the LS mean change in HbA1c at week 36 from baseline was similar between the two treatment arms. The Applicant's results are shown in Table 23. The LS means difference in HbA1c change from baseline between the two treatment arms was 0.01 (95% CI: -0.085, 0.101). The Applicant did not find this

difference to be statistically significant and confirmed these findings by analyzing the PP population using the same ANCOVA model used for the mITT population analysis. The confirmation analysis using the PP population found the LS means difference in HbA1c change from baseline between the two treatment arms to be 0.01 (95% CI: -0.089, 0.101). These results do not indicate there is a difference in efficacy between MYL-1501D and U.S.-Lantus, nor do they preclude a demonstration of biosimilarity or interchangeability between MYL-1501D and U.S.-Lantus.

**Table 23. Statistical Analysis (ANCOVA) of Change in HbA1c (%) from Baseline to Week 36 Primary Analysis (Modified Intent-to-Treat Population)**

| Change in HbA1c from Baseline (%) | U.S.-Lantus N = 57 | Switching Arm N = 61 | Switching Arm – U.S. Lantus Arm* |
|---|---|---|---|
| N | 57 | 61 | |
| LS mean (SE) | -0.06 (0.034) | -0.05 (0.032) | |
| 95% CI | -0.126, 0.007 | -0.115, 0.012 | |
| LS means difference (SE) | | | 0.01 (0.047) |
| 95% CI for LS mean difference | | | -0.085, 0.101 |

Abbreviations: N = number of patients in the analysis; ANCOVA = analysis of covariance; HbA1c = glycosylated hemoglobin; CI = confidence interval; LS = least squares; mITT = modified Intent-to-Treat; SE = standard error.
*Switching arm minus U.S. Lantus arm
Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, Table 11-3

The Applicant also confirmed the results of the primary analysis using the ITT population. As stated earlier, the Applicant used a REML-based MMRM approach to analyze this population. The Applicant's analysis found the LS means difference in HbA1c change from baseline at week 36 between the two treatment arms to be 0.03 (95% CI: -0.132, 0.193). These results are shown below in Table 24.

**Table 24. Statistical Analysis of Change in HbA1c (%) from Baseline to Week 36 – Sensitivity Analysis (ITT Population using MMRM)**

| Change in HbA1c from Baseline (%) Sensitivity Analysis | U.S.-Lantus N = 63 | Switching arm N = 64 | Switching Arm – U.S. Lantus Arm* |
|---|---|---|---|
| N | 63 | 64 | |
| LS mean (SE) | -0.05 (0.059) | -0.02 (0.057) | |
| 95% CI | (-0.163, 0.069) | (-0.129, 0.097) | |
| LS means difference (SE) | | | 0.03 (0.082) |
| 95% CI for LS mean difference | | | (-0.132, 0.193) |

Abbreviations: N = number of patients in the analysis; CI = confidence interval; HbA1c = glycosylated hemoglobin; LS = lease squares; ITT: Intent-to-Treat; MMRM = mixed-effects model approach; SE = standard error
*Switching arm minus U.S. Lantus armSource: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, Table 11-5

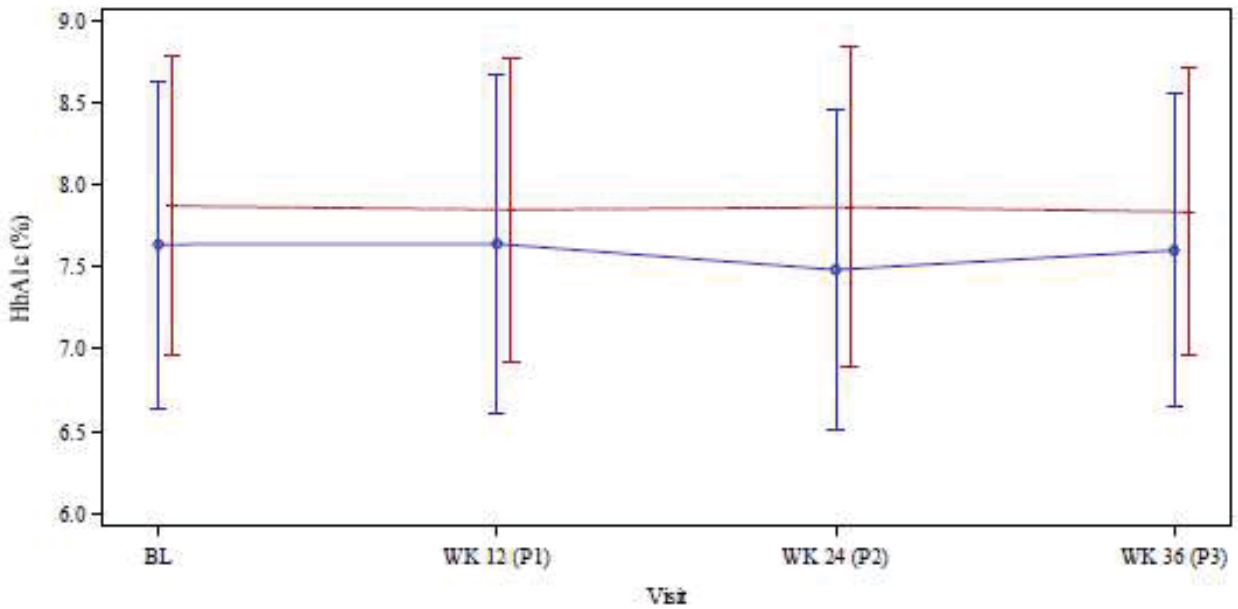
### Potential Effects of Missing Data

The Applicant did not impute missing primary and secondary efficacy and safety analyses data except when the week 36 HbA1c value was missing on account of early discontinuation. In this case, the exit measurement of Period 3 was used instead. Given the high retention rate in this study, this was unlikely to have a large effect on the analyses and does not interfere with the review's objective of ensuring that the data do not preclude a demonstration of biosimilarity or interchangeability.

### Analysis of Secondary Clinical Endpoint(s)

Secondary clinical endpoint analyses were performed on multiple endpoints. The Applicant evaluated the change in HbA1c from baseline at each scheduled visit using the ITT population. The Applicant's analysis found that HbA1c remained relatively stable in both treatment arms despite the switching of products in the switching treatment arm. The Applicant's analysis did not find any nominally statistically significant changes (p-value < 0.05) in HbA1c from baseline in either treatment arm at any of the three measured timepoints nor did the Applicant find any nominally statistically significant treatment differences at any time point. The HbA1c value over time in each treatment arm is illustrated in Figure 11.

**Figure 11. Mean (± SD) Actual HbA1c (%) over Time by Treatment (Intent-to-Treat Population)**




Abbreviations: HbA1c = glycosylated hemoglobin; BL = baseline, week 0; WK 12 (P1) = Weeks 1, 4, 8, and 12; WK 24 (P2) = Weeks 14, 16, 20, and 24; WK 36 (P3) = Week 26, 28, 32, and 36

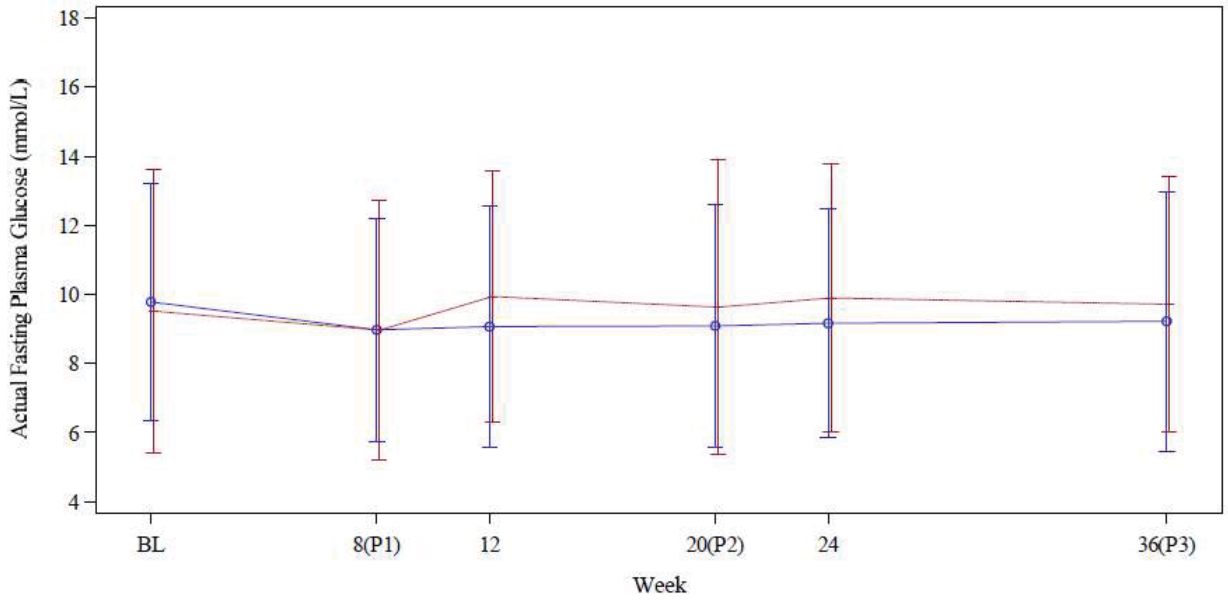
= switching = U.S.-Lantus

Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, Figure 11-1

### Fasting plasma glucose

The Applicant also measured fasting plasma glucose (FPG) values at scheduled visits and compared the two treatment arms. The Applicant's analysis found the measured FPG values remained stable throughout the three treatment Periods for both treatment arms. There were no nominally statistically significant changes ($p < 0.05$) in FPG values from baseline in either treatment arm and no nominally statistically significant treatment differences in FPG values between treatment arms at any time point. Any noted differences in glucose values between the two treatment arms were not clinically relevant. Figure 12 illustrates the mean FPG in each treatment arm over time.

**Figure 12. Mean (± SD) of the Actual Fasting Plasma Glucose by Visit and Treatment (Intent-to-Treat Population)**




Abbreviations: SD = standard deviation; BL = baseline, week 0; (P1) = Weeks 1, 4, 8, and 12; (P2) = Weeks 14, 16, 20, and 24; (P3) = Week 26, 28, 32, and 36

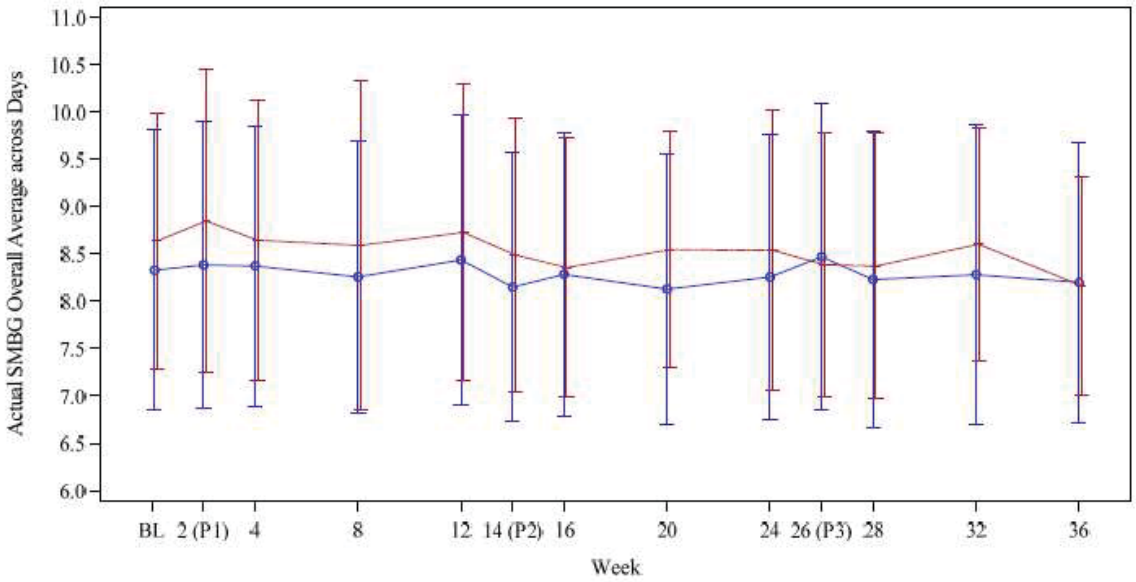
= switching = U.S.-Lantus

Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, Figure 11-3

### Self-Monitored Blood Glucose

The Applicant also examined change in 8-point self-monitored blood glucose (SMBG) levels from baseline at scheduled visits and compared the two treatment arms. The Applicant found there were no nominally statistically significant differences ($p < 0.05$) in SMBG between any treatment visit and baseline in the switching treatment arm. In the U.S.-Lantus treatment arm, there were no nominally statistically significant changes in SMBG between any treatment visit and baseline except for week 36. The change from baseline was -0.426 ± 1.1243 mmol/L; $p = 0.007$. This difference in blood glucose is not meaningful. The Applicant also noted that there were no nominally statistically significant differences in SMBG change from baseline value between treatment arms at any time point during the study. The average SMBG in each treatment arm over time is shown below inFigure 13

**Figure 13. Mean (± SD) of the Actual Overall SMBG (mmol/L) Average by Visit and Treatment (Intent-to-Treat Population)**




Abbreviations: SMBG = self-monitored blood glucose; SD = standard deviation; BL = baseline, week 0; (P1) = Weeks 1, 4, 8, and 12; (P2) = Weeks 14, 16, 20, and 24; (P3) = Week 26, 28, 32, and 36

= switching = U.S.-Lantus

Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, from Figure 11-4

**Daily Insulin Dose**

Finally, the Applicant examined the change in daily insulin dose/unit body weight for days of 8-point SMBG profile documentation. The Applicant found the baseline total daily insulin dose (TDD) was 0.68 ± 0.24 U/kg in the switching arm and 0.72 ± 0.25 U/kg in the U.S.-Lantus arm. The Applicant's analysis found the mean TDD remained relatively stable throughout the study with no nominally statistically significant changes from baseline in either treatment arm and no nominally statistically significant differences in the change from baseline between treatment arms.

When the Applicant evaluated the results of mean basal insulin dose, it was revealed that the mean baseline basal insulin dose was lower in the switching arm (0.31 ± 0.12 U/kg) compared to the U.S.-Lantus arm (0.36 ± 0.18 U/kg) and remained lower throughout the study. The Applicant's analysis found the mean basal insulin dose was higher than baseline at all time points in the switching arm with nominally statistically significant increases noted at weeks 4, 8, 20, 24, and 36. There were no statistically significant changes in the basal insulin dose at any time period from baseline in the U.S.-Lantus arm. However, the difference between the two treatment arms in mean change from baseline in basal insulin dose was nominally statistically significant at only one timpoint (week 36), at which time the difference in the change was 0.019 U/kg (95% CI: 0.007, 0.031; p = 0.002).

The clinical reviewer focused on the data from the Applicant's clinical study report that showed the mean basal insulin dose in the switching arm over time. As shown below in Table 25, the basal insulin dose did not change in a meaningful way in the switching

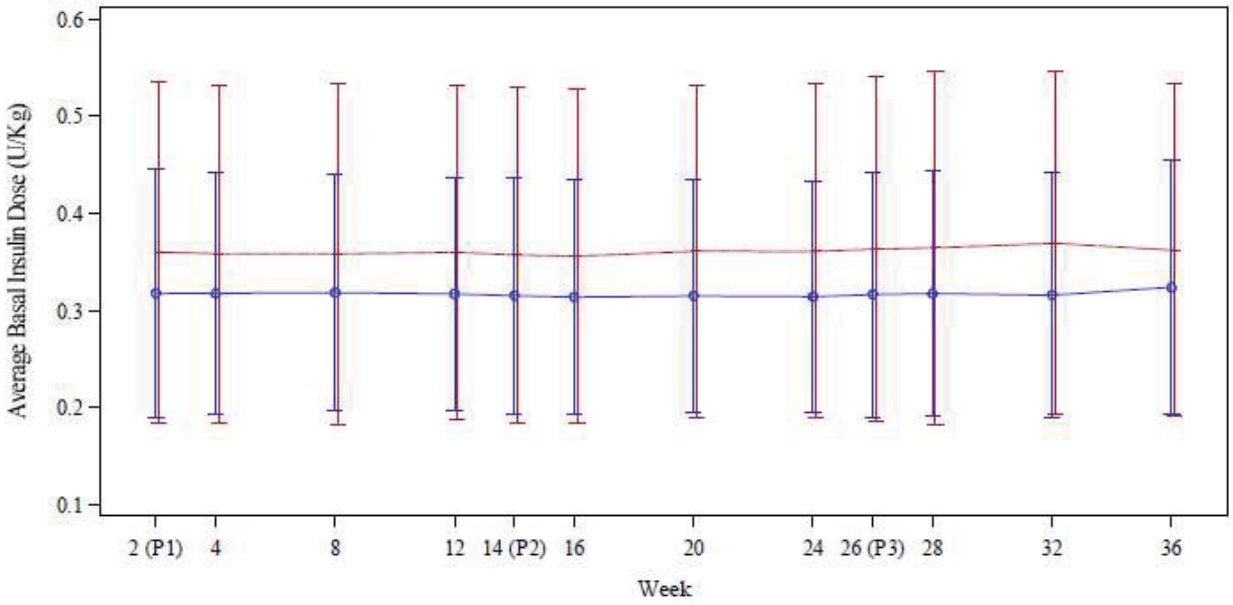
treatment arm when MYL-1501D was switched to U.S.-Lantus and then back to MYL-1501D. The mean basal insulin dose at specified visits for this treatment arm is shown graphically in Figure 14 in the blue line. These results do not indicate that there is a difference in potency between treatment arms nor do they preclude a demonstration of biosimilarity or interchangeability between MYL-1501D and U.S.-Lantus.

**Table 25. Mean Basal Insulin Dose and Mean Change from Baseline in Insulin Basal Dose in the ITT Population switching Treatment Arm by Treatment Visit**

| Treatment Week (Period) | Insulin dose U/kg (SD) | Mean Change from Baseline U/kg (SD) | P value |
|---|---|---|---|
| Baseline | 0.3107 (0.11815) | | |
| Week 2 (Period 1) | 0.3172 (0.12737) | 0.0066 (0.02948) | 0.085 |
| Week 4 (Period 1) | 0.3175 (0.12401) | 0.0067 (0.02271) | 0.022 |
| Week 8 (Period 1) | 0.3181 (0.12137) | 0.0074 (0.02606) | 0.027 |
| Week 12 (Period 1) | 0.3168 (0.12045) | 0.0061 (0.02720) | 0.080 |
| **Week 14 (Period 2)** | **0.3150 (0.12188)** | **0.0045 (0.03340)** | **0.288** |
| **Week 16 (Period 2)** | **0.3135 (0.12025)** | **0.0065 (0.02726)** | **0.070** |
| **Week 20 (Period 2)** | **0.3147 (0.11957)** | **0.0080 (0.02555)** | **0.016** |
| **Week 24 (Period 2)** | **0.3140 (0.11959)** | **0.0074 (0.02766)** | **0.040** |
| Week 26 (Period 3) | 0.3162 (0.12643) | 0.0095 (0.03953) | 0.066 |
| Week 28 (Period 3) | 0.3173 (0.12678) | 0.0105 (0.04129) | 0.054 |
| Week 32 (Period 3) | 0.3155 (0.12630) | 0.0082 (0.04383) | 0.150 |
| Week 36 (Period 3) | 0.3237 (0.13096) | 0.0163 (0.04277) | 0.004 |

Abbreviations: SD = standard deviation; ITT = intent-to-treat
Unbolded text: Corresponds to the treatment Periods during which the basal insulin glargine product was MYL-1501D
**Bolded text: Corresponds to the treatment Period during which the basal insulin glargine product was U.S.-Lantus**
Source: Created by clinical reviewer using data from the Applicant's Clinical Study Report for MYL-1501D-3003, Table 14.2.2.4

**Figure 14. Mean (± SD) of the Actual Average Basal Insulin Dose by Visit and Treatment (Intent-to-Treat Population)**




Abbreviations: SD = standard deviation; (P1) = Weeks 1, 4, 8, and 12; (P2) = Weeks 14, 16, 20, and 24; (P3) = Week 26, 28, 32, and 36

= switching = U.S.-Lantus

Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, Figure 11-6

Finally, the Applicant calculated the average total daily prandial dose of insulin at specified visits in both treatment arms. At baseline, the mean total daily prandial insulin dose was 0.37 ± 0.16 U/kg in the switching arm and 0.36 ± 0.15 U/kg in the U.S.-Lantus arm. The only nominally statistically significant change from baseline in mean total daily prandial insulin dose in either group that the Applicant's analysis found occurred in the switching arm at week 20, at which time the mean change from baseline was -0.026 ± 0.074 units/kg (p = 0.009). This result does not preclude a demonstration of biosimilarity or interchangeability.

*Reviewer comment: Although the Applicant compared doses across study arms in a variety of ways at a number of timepoints, no specific hypotheses were formally tested. For that reason, the statistical comparisons are descriptive rather than inferential. In the context of a large number of comparisons, the occasional finding of nominally statistically significant differences across study arms do not necessarily support a conclusion that a difference exists and thus these results do not preclude a demonstration of biosimilarity or interchangeable.*

**Other Clinical Endpoints**

No exploratory endpoints were analyzed.

### 13.5.2. Review of Safety Data

**Methods**

The patient population included, and the dose and dose frequency evaluated in study MYL-1501D-3003 are representative of the intended patient population, dose, and dose frequency for use of MYL-1501D, respectively.

The review of safety data from study MYL-1501D-3003 used the datasets provided by the Applicant and analyzed the safety population. The Applicant defined the safety population as randomized patients who took at least one dose of the study product. If there was any doubt whether a patient received a dose of the study product, the Applicant included the patient in this population. In addition to analyses of the standard safety assessments, this review also focused on the known safety issues with insulin such as hypoglycemia and device malfunction.

The Applicant's definition of the safety population was appropriate. In total, 127 patients were part of the safety analysis set. 64 patients received at least one dose of MYL-1501D and 63 patients received at least one dose of U.S.-Lantus. The results of this study's safety analyses were compared to the safety analyses performed previously by FDA on studies comparing MYL-1501D and U.S.-Lantus, mainly, MYL-GAI-3001 and MYL-GAI-3002.

**Categorization of Adverse Events**

The Applicant defined an adverse event (AE) as any untoward medical occurrence, such as a clinically important lab finding, symptom or disease, temporarily associated with drug product administration in a clinical investigation patient that does not necessarily have a causal relationship with the product. This definition also included exacerbation of pre-existing medical conditions. An AE was considered a treatment emergent adverse event (TEAE) if the first onset occurred after randomization and the first administration of the study product (either MYL-1501D or U.S.-Lantus) through the follow-up visit or 28 days after the last dose (for those who did not have a follow-up visit).

A serious adverse event (SAE) was defined as any untoward medical event at any dose of the study product that resulted in death, was life threatening, resulted in persistent or significant disability, was a congenital anomaly, was an important medical event, or required an inpatient hospitalization or prolongation of hospitalization.

At the week 0 visit, patients learned the definition of an AE and were instructed to record these in their diary in a timely manner if they experienced one. AEs were collected from patient diaries and through questioning with open ended questions such as "How are you feeling?" The Investigator recorded these AEs at each study visit.

Adverse events were categorized using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. The Investigator graded the severity of AEs according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. The grading scheme is shown in Table 26.

**Table 26. Definitions Used to Categorize the Severity of an AE**

| Grade | Definition |
|---|---|
| Grade 1 – MILD | Does not interfere with patient's usual function |
| Grade 2 – MODERATE | Interferes to some extent with patient's usual function |
| Grade 3 – SEVERE | Interferes significantly with patient's usual function |
| Grade 4 – LIFE-THREATENING | Risk of death at time of event |
| Grade 5 – DEATH | Death related to AE |

Abbreviations: AE = adverse event
Source: Adapted from the Applicant's Clinical Study Protocol for MYL-1501D-3003, Table 6: Clinical Severity of Adverse Events

**Safety Analyses**

This review compared the safety of the switching arm to the U.S.-Lantus arm by analyzing the safety data from study MYL-1501D-3003. The review tools used to conduct independent reviewer analyses included MAED, JMP Clinical, JMP, and OCS Toolbox Demographic Tool.

The following analyses were conducted to compare the safety of the two treatment arms:

- Incidence of TEAEs, SAEs, and TEAEs ≥ Grade 3 in severity
- Hypoglycemia incidence and 30-day event rates
- Incidence of device related safety events
- Other analyses
    - Vital signs
    - ECG
    - Laboratory data

### 13.5.3. Major Safety Results

**Relevant Characteristics of the Population Evaluated for Safety**

All patients in the randomized population were included in the safety population. The demographics were shown in Table 21 and discussed earlier.

**Exposure**

Table 27 summarizes the exposure of the safety population to the study products in study MYL-1501D-3003. The mean (SD) duration of exposure was comparable between

the treatment arms: 245.9 (31.4) days in the U.S.-Lantus arm and 251.1 (16.81) days in the switching arm. The extent of exposure was also similar between the two treatment arms within each treatment Period.

**Table 27. Summary of Exposure to Investigational Product (Safety Population)**

| | | | Switching Arm – U.S.-Lantus Arm | | |
|---|---|---|---|---|---|
| **Drug Administration Details** | **U.S.-Lantus N = 63** | **Switching arm N = 64** | **LS Means Difference (SE)** | **95% CI for LS Means Difference** | **P-Value** |
| Overall Duration of Exposure (Days) | | | | | |
| N | 63 | 64 | | | |
| Mean | 245.9 | 251.1 | | | |
| Standard | 31.40 | 16.81 | | | |
| Minimum | 93 | 144 | | | |
| Median | 253.0 | 252.0 | | | |
| Maximum | 282 | 274 | | | |
| | | | 5.0 (4.45) | (-3.8, 13.8) | .266 |
| Period 1 Duration of Exposure (Days) | | | | | |
| N | 62 | 63 | | | |
| Mean | 85.0 | 84.1 | | | |
| Standard | 5.52 | 4.38 | | | |
| Minimum | 71 | 76 | | | |
| Median | 84.0 | 84.0 | | | |
| Maximum | 104 | 98 | | | |
| | | | -0.9 (0.89) | (-2.7, 0.9) | .316 |
| Period 2 Duration of Exposure (Days) | | | | | |
| N | 57 | 62 | | | |
| Mean | 72.9 | 72.1 | | | |
| Standard | 5.69 | 5.41 | | | |
| Minimum | 56 | 53 | | | |
| Median | 74.0 | 73.0 | | | |
| Maximum | 91 | 84 | | | |
| | | | -0.8 (1.02) | (-2.8, 1.2) | .443 |

| | | | | | |
|---|---|---|---|---|---|
| Period 3 Duration of Exposure (Days) | | | | | |
| N | 57 | 61 | | | |
| Mean | 73.1 | 73.5 | | | |
| Standard | 7.18 | 5.09 | | | |
| Minimum | 57 | 60 | | | |
| Median | 73.0 | 73.0 | | | |
| Maximum | 99 | 85 | | | |
| | | | 0.4 (1.14) | (-1.9, 2.7) | .729 |

Abbreviations: CI = confidence interval; LS = least squares; N = total number of patients in Safety Population in each treatment group; SE = standard error
Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003, Table 12-1: Summary of Exposure to Study Drug (Safety Population)

**Other Product-Specific Safety Concerns**

The Applicant collected patient vital signs, laboratory measurements, and ECG findings as part of the safety assessment. There were no meaningful differences between treatment arms for change from baseline in laboratory parameters, weight, or vital signs at any time point during the study. None of the study patients' ECG results shifted from baseline to abnormal clinically significant at any on-treatment assessment.

**Deaths**

One death was reported during study MYL-1501D-3003. A patient randomized to the U.S.-Lantus arm died on study day 94 as a consequence of SAE of injury. She was a pedestrian hit by a drunk driver near her home. She died at the scene. No autopsy was performed. The investigator considered her death unrelated to the study product. These findings do not preclude a determination of biosimilarity or interchangeability.

**Treatment Emergent Adverse Events**

The proportion of patients who experienced any TEAE was similar between the two treatment arms. This was also true for TEAEs ≥ Grade 3 in severity. There was a slight numeric imbalance in patients experiencing a treatment emergent SAE in the U.S.-Lantus arm compared to the switching arm, however, the overall findings do not indicate a difference across treatment arms. Table 28 summarizes the number and proportion of patients in each treatment arm who experienced a TEAE at any time during the study.

**Table 28. Summary of TEAEs Between Treatment Groups Throughout the Entire Study (Safety Population)**

| | U.S.-Lantus (N = 63) | Switching arm (N = 64) |
|---|---|---|
| **Event** | **n (%)** | **n (%)** |

| | | |
|---|---|---|
| Any TEAE | 42 (66.67) | 41 (64.06) |
| Treatment emergent SAE | 5 (7.94) | 2 (3.13) |
| TEAE ≥ Grade 3 in Severity | 3 (4.76) | 2 (3.13) |
| TEAE leading to death | 1 (1.59) | 0 (0) |
| TEAE leading to permanent treatment discontinuation | 1 (1.59) | 0 (0) |

Abbreviations: N = total arm population; n = number of individual patients; TEAE = treatment emergent adverse event; SAE = serious adverse event
Source: Table generated by clinical reviewer using ADAE And ADSL datasets

Table 29 shows TEAE preferred terms (PTs) organized by system organ class (SOC) that occurred in ≥ 2% of all patients in the safety population throughout the study. The most common TEAE SOC was infections and infestations, occurring in 37.8% of the total safety population. There were more infections in the U.S.-Lantus arm than the switching arm, but the difference was small. When infections were further analyzed by PT, there were no large differences in any one PT between the two treatment arms. Any differences seen are likely due to chance.

It is notable that three times as many patients in the U.S.-Lantus arm experienced an eye disorder compared to the switching arm. This difference was largely driven by events of diabetic retinopathy. However, when reviewing the number of patients experiencing this event, the difference is small, and the number of patients is low.

The TEAEs were further analyzed by treatment Period between the two treatment arms and are shown in Table 30, Table 31, and Table 32**Error! Reference source not found.**. The TEAEs within each treatment Period were similar to the TEAEs in the overall study and there were no notable differences between the two treatment arms. Overall, these findings do not indicate a difference across treatment arms and do not preclude a determination of biosimilarity or interchangeability.

**Table 29. TEAEs Preferred Terms with ≥ 2% Occurrence in the Total Safety Population Organized by System Organ Class**

| | **U.S.-Lantus (N = 63)** | **Switching arm (N = 64)** | **Total (N = 127)** |
|---|---|---|---|
| System Organ Class* Preferred Term | n (%) | n (%) | n (%) |
| **Infections and infestations** | **25 (39.7)** | **23 (35.9)** | **48 (37.8)** |
| Upper respiratory tract infection | 5 (7.9) | 7 (10.9) | 12 (9.4) |
| Nasopharyngitis | 4 (6.3) | 3 (4.7) | 7 (5.5) |
| Influenza | 2 (3.2) | 3 (4.7) | 5 (3.9) |
| Gastroenteritis viral | 2 (3.2) | 2 (3.1) | 4 (3.1) |
| Herpes zoster | 3 (4.8) | 0 | 3 (2.4) |
| Bronchitis | 2 (3.2) | 1 (1.6) | 3 (2.4) |
| Sinusitis | 1 (1.6) | 2 (3.1) | 3 (2.4) |

| | | | |
|---|---|---|---|
| **Injury, poisoning and procedural complications** | **8 (12.7)** | **7 (10.9)** | **15 (11.8)** |
| Muscle strain | 2 (3.2) | 2 (3.1) | 4 (3.1) |
| **Gastrointestinal disorders** | **4 (6.3)** | **7 (10.9)** | **11 (8.7)** |
| Diarrhoea | 1 (1.6) | 2 (3.1) | 3 (2.4) |
| **Respiratory, thoracic, and mediastinal disorders** | **6 (9.5)** | **3 (4.7)** | **9 (7.1)** |
| Oropharyngeal pain | 2 (3.2) | 1 (1.6) | 3 (2.4) |
| **Eye disorders** | **6 (9.5)** | **2 (3.1)** | **8 (6.3)** |
| Diabetic retinopathy | 4 (6.3) | 1 (1.6) | 5 (3.9) |
| **Immune system disorders** | **1 (1.6)** | **3 (4.7)** | **4 (3.1)** |
| Seasonal allergy | 1 (1.6) | 3 (4.7) | 4 (3.1) |

Abbreviations: N = total arm population; n = number of individual patients; TEAE = treatment emergent adverse event
*Total of all preferred terms including preferred terms with ≤ 2% occurrence in total study population
Source: Table generated by clinical reviewer using ADAE and ADSL datasets provided

**Table 30. Period 1 TEAE Preferred Terms with ≥ 2% Occurrence in the Total Safety Population Organized by System Organ Class**

| | U.S.-Lantus (N = 63) | Switching arm (N = 64) | Total (N = 127) |
|---|---|---|---|
| System Organ Class<br>Dictionary Derived Term | n (%) | n (%) | n (%) |
| **Infections and infestations** | | | |
| Upper respiratory tract infection | 3 (4.8) | 2 (3.1) | 5 (3.9) |
| Nasopharyngitis | 2 (3.2) | 2 (3.1) | 4 (3.1) |
| Gastroenteritis viral | 2 (3.2) | 1 (1.6) | 3 (2.4) |
| Sinusitis | 1 (1.6) | 2 (3.1) | 3 (2.4) |
| **Injury, poisoning and procedural complications** | | | |
| Muscle strain | 1 (1.6) | 2 (3.1) | 3 (2.4) |
| **Eye disorders** | | | |
| Diabetic retinopathy | 4 (6.3) | 1 (1.6) | 5 (3.9) |

Abbreviations: N = total arm population; n = number of individual patients; TEAE = treatment emergent adverse event
Source: Table generated by clinical reviewer using ADAE And ADSL datasets provided

**Table 31. Period 2 TEAE Preferred Terms with ≥ 1%* Occurrence in the Total Safety Population Organized by System Organ Class**

| | U.S.-Lantus (N = 63) | Switching arm (N = 64) | Total (N = 127) |
|---|---|---|---|
| System Organ Class<br>Dictionary Derived Term | n (%) | n (%) | n (%) |
| **Infections and infestations** | | | |

| | | | |
|---|---|---|---|
| Influenza | 1 (1.6) | 1 (1.6) | 2 (1.6) |
| Nasopharyngitis | 1 (1.6) | 1 (1.6) | 2 (1.6) |
| Upper respiratory tract infection | 2 (3.2) | 0 | 2 (1.6) |

Abbreviations: N = total arm population; n = number of individual patients; TEAE = treatment emergent adverse event
*There were no TEAE preferred terms that occurred in ≥ 2% of the total safety population
Source: Table generated by clinical reviewer using ADAE And ADSL datasets provided

**Table 32. Period 3 TEAE Preferred Terms with ≥ 2% Occurrence in the Total Safety Population Organized by System Organ Class**

| | U.S.-Lantus (N = 63) | Switching arm (N = 64) | Total (N = 127) |
|---|---|---|---|
| System Organ Class<br>Dictionary Derived Term | n (%) | n (%) | n (%) |
| **Infections and infestations** | | | |
| Upper respiratory tract infection | 2 (3.2) | 5 (7.8) | 7 (5.5) |
| **Gastrointestinal disorders** | | | |
| Diarrhoea | 1 (1.6) | 2 (3.1) | 3 (2.4) |

Abbreviations: N = total arm population; n = number of individual patients; TEAE = treatment emergent adverse event
Source: Table generated by clinical reviewer using ADAE And ADSL datasets provided

**Serious Adverse Events**

The serious adverse events (SAE) analyses did not reveal any new or different safety when comparing both treatment arms. Table 33 shows all the SAEs reported in study MYL-1501D-3003. All 3 SAEs in the switching treatment arm occurred during treatment Period 2 when the patients were taking U.S.-Lantus.

The same patient experienced SAEs “myocardial infarction” and “cerebrovascular accident.” The event narratives revealed that the patient experienced the myocardial infarction first. The patient was hospitalized, underwent an angioplasty, received three stents, and was discharged home. Eight days later, the patient experienced a cerebrovascular accident and was readmitted to the hospital. The patient’s past medical history included hypercholesterolemia, hypertension, and type 1 diabetes. These medical comorbidities are risk factors for arterial disease. These results do not indicate a difference across treatment arms when comparing both treatment arms.

**Table 33. SAEs By Preferred Term**

| | U.S.-Lantus (N = 63) | Switching arm (N = 64) |
|---|---|---|
| **Preferred Term** | n (%) | n (%) |
| Basal cell carcinoma* | 1 (1.6) | |
| Bladder cancer* | 1 (1.6) | |

| | | |
|---|---|---|
| Myocardial infarction* | | 1 (1.6) |
| Retinal detachment** | 1 (1.6) | |
| Cholecystitis acute* | | 1 (1.6) |
| Injury*** | 1 (1.6) | |
| Ketoacidosis* | 1 (1.6) | |
| Cerebrovascular accident* | | 1 (1.6) |

Abbreviations: N = total arm population; n = number of individual patients; SAE = serious adverse event
* Final outcome was recovered/resolved
** Final outcome was recovered/resolved with sequelae
*** Final outcome was fatal
Source: Table generated by clinical reviewer using ADAE And ADSL datasets provided

**Treatment Emergent Adverse Events Grade 3 or Higher**

A similar proportion of patients in each treatment arm experienced a TEAE ≥ Grade 3 in severity as judged by the Investigator: 3 (4.76%) patients in the U.S.-Lantus arm and 2 (3.13%) patients in the MYL-1501D arm. The TEAEs are shown below in Table 34. The number of TEAEs considered ≥ Grade 3 in severity was higher in the U.S.-Lantus arm compared to the switching arm.

However, the TEAEs hypocalcaemia, hypokalaemia, influenza, ketoacidosis, and oesophagitis ulcerative all occurred in the same patient on the same day. These events also occurred after the end of treatment visit, prior to the follow up visit, during which time the patient was not using the study product. Though these events could be considered related to the study product, it is more likely that the lab abnormalities are related to the patient's underlying influenza infection.

The investigator determined that the TEAE "pruritis generalised" was probably related to the study product. After review of the narrative, this is difficult to determine with certainty. The patient experienced this event after administrating MYL-1501D. The symptoms worsened after an additional dose. The patient stopped MYL-1501D and switched to pharmacy dispensed Lantus which resulted in resolution of the symptoms. The patient continued taking pharmacy dispensed Lantus for the remainder of the study. Importantly, however, the adverse event causality was confounded by possible exposure to cat scratches from the patient's pet cats.

It is important to note that the unblinded Investigators determined the severity of the TEAEs. Although the Applicant provided definitions of how to grade severity, determining the severity of a TEAE can be subjective. The Applicant provided case report forms, narratives, and event summaries in the clinical study report summarizing the TEAEs graded ≥ 3 in severity. After review of these narratives, these data do not suggest a difference across treatment arms.

**Table 34. All TEAEs Preferred Terms Classified as CTCAE Grade ≥ 3 in Severity**

| | U.S.-Lantus | Switching arm |
|---|---|---|

| | (N = 63) | (N = 64) |
|---|---|---|
| **Preferred Term** | n (%) | n (%) |
| Hypocalcaemia* | 1 (1.6) | |
| Hypokalaemia* | 1 (1.6) | |
| Ketoacidosis* | 1 (1.6) | |
| Retinal detachment* | 1 (1.6) | |
| Retinopathy* | 1 (1.6) | |
| Myocardial infarction* | | 1 (1.6) |
| Oesophagitis ulcerative* | 1 (1.6) | |
| Influenza* | 1 (1.6) | |
| Injury** | 1 (1.6) | |
| Cerebrovascular accident* | | 1 (1.6) |
| Pruritus generalised* | | 1 (1.6) |

Abbreviations: N = total arm population; n = number of individual patients; TEAE = treatment emergent adverse event; CTCAE = Common Terminology Criteria for Adverse Events Version 4.03
* Grade 3
** Grade 5
Source: Table generated by clinical reviewer using ADAE And ADSL datasets provided

**Dropouts and/or Discontinuations**

Two patients discontinued the study medication secondary to an adverse event. The first patient discontinued the study medication on account of death. This patient's death was described earlier. The second patient experienced generalized pruritis thought to be probably related to MYL-1501D. This patient's event was also described earlier. The Applicant did not consider this a TEAE leading to permanent treatment discontinuation, but review of the event suggests otherwise. Because of the patient's symptoms, they stopped MYL-1501D and switched to pharmacy-dispensed Lantus. This suggests that the TEAE did lead to treatment discontinuation. However, after review of the narratives surrounding these events, these data do not suggest a difference across treatment arms.

### 13.5.4. Additional Safety Evaluations

**Hypoglycemia Events**

Hypoglycemia is a clinically significant event that is a common adverse effect of insulin products. The Applicant evaluated hypoglycemia event rates per 30 days in each treatment arm and used the following definitions to classify hypoglycemia events:

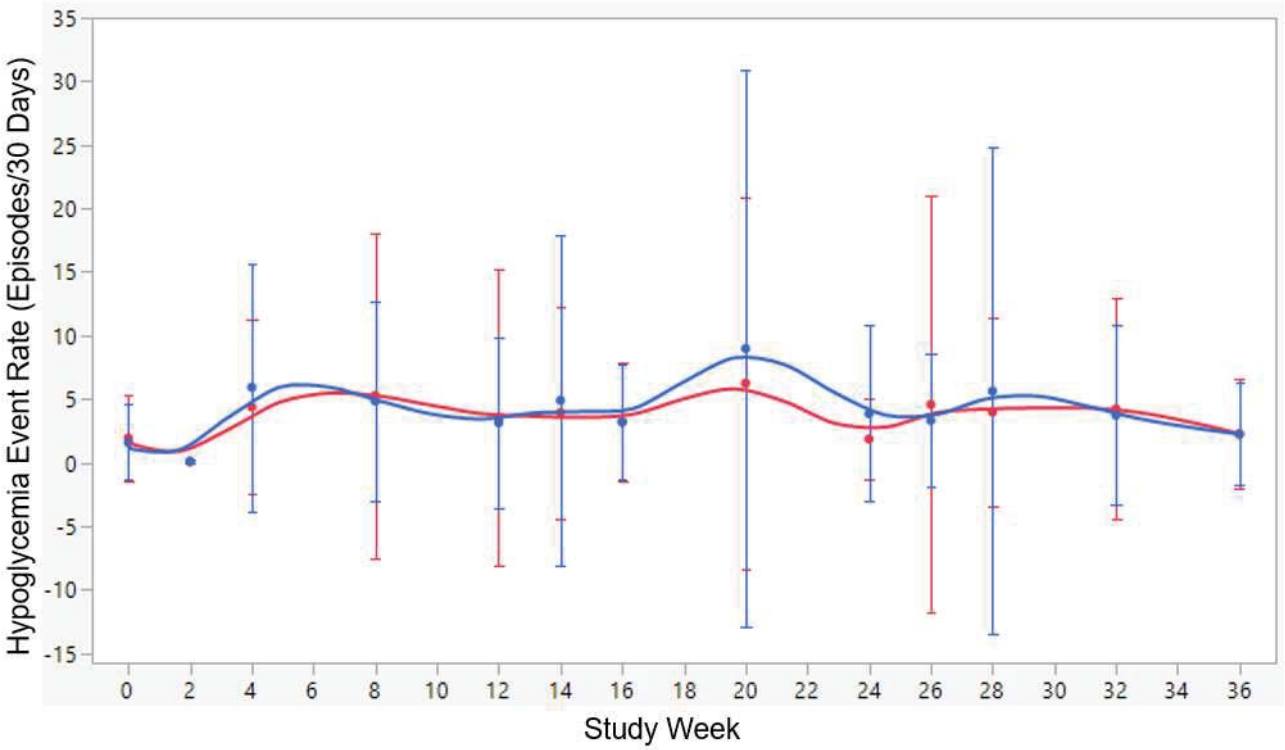
- Severe hypoglycemia: requires the assistance of another person to administer carbohydrates, glucagon, or other resuscitative actions which results in neurological recovery regardless of the availability of a blood sugar measurement
- Symptomatic hypoglycemia: typical symptoms of hypoglycemia accompanied by measured plasma glucose ≤ 70 mg/dL

- Asymptomatic hypoglycemia: no characteristic symptoms of hypoglycemia but a measured plasma glucose ≤ 70 mg/dL
- Probable symptomatic hypoglycemia: characteristic hypoglycemia symptoms with no blood glucose level that resolves with food intake, subcutaneous glucagon, or intravenous glucose
- Relative hypoglycemia: typical symptoms of hypoglycemia but measured plasma glucose > 70 mg/dL
- Nocturnal hypoglycemia: hypoglycemia that occurs from the time the patient goes to bed at night until the time he or she wakes up; may include any of the above definitions

The Applicant defined the incidence of hypoglycemic events during a particular time period as the number of patients experiencing at least one hypoglycemic event within that time period. Overall, 58 (90.6%) of the patients in the switching arm and 57 (90.5%) of the patients in the U.S.-Lantus arm experienced at least one of the hypoglycemic events described above during the study.

The Applicant calculated the 30-day hypoglycemia event rate for each patient by totaling the number of hypoglycemic events between 2 visits, dividing that value by the number of days between those visits, and then multiplying that number by 30. Figure 15 shows the mean 30-day hypoglycemia event rates in each treatment arm throughout the study. These hypoglycemia event rates include all definitions of hypoglycemia described above. The hypoglycemia event rates are similar between treatment arms. The Applicant did not find any statistically significant differences in hypoglycemia event rate change from baseline between the two arms. The largest difference in hypoglycemia event rates between the two treatment arms occurred at week 20. However, this is when the patients in the switching arm were using U.S.-Lantus, so the difference in hypoglycemia event rates may not be related to the study products. Nocturnal hypoglycemia 30-day event rates were similar to the overall hypoglycemia event rates. None of the hypoglycemic episodes met the definition of severe hypoglycemia.

**Figure 15. Mean (± SD) 30 Day Hypoglycemia Event Rates for Each Treatment Visit Over the Course of the Study by Treatment Arm (Safety Population)**




Abbreviations: SD = standard deviation

= switching = U.S.-Lantus

Source: Graph created by clinical reviewer using ADHYSUM dataset

**Device Safety**

In total, 8 patients experienced device difficulties, 4 in each treatment arm. Table 35 displays the device malfunction descriptions verbatim from the Applicant's dataset for the 8 patients. Based on the verbiage, it appears 2 patients experienced difficulties with the Humalog pen and 2 patients experienced difficulties with the glucometer (i.e., at least 4 of the 8 events reported did not involve either the MYL-1501D pen device or the U.S.-Lantus pen device).

Based on the verbatim description from the applicant, all of the 4 patients who experienced device difficulties that appear to have been with a pen not identified as the Humalog pen were in the switching arm. As shown below, only 2 of these events occurred during Period 1 when the patients were using the MYL-1501D pen device. One subject dropped the pen and broke the cartridge holding the insulin. The other patient noted a problem with the needle, resulting in a dosing error. The patient attempted to administer 34 units of MYL-1501D but received only 14 units. However, a pen needle issue was also noted during Period 2 in the switching arm when patients were not using the MYL-1501D pen device suggesting pen needle issues are not specific to the MYL-1501D pen device. The fourth reported event "2 syringes does not work" also occurred during Period 2 in when patients were not using the MYL-1501D pen device. No reported device malfunction resulted in the report of an adverse event.

**Table 35. Reported Device Malfunctions in Safety Population**

| | U.S.-Lantus (N = 63) | Switching arm (N = 64) |
|---|---|---|
| **Description of Device Malfunction** | **n (%)** | **n (%)** |
| **Period 1** | | |
| The subject dropped 1 pen and broke the cartridge holding the insulin | | 1(1.6) |
| Mylan glargine needle malfunction, subject needed 34 units and it only gave 14 units | | 1(1.6) |
| **Period 2** | | |
| 2 syringes does not work | | 1 (1.6) |
| Humalog pen would not dispense full dose when dialed | 1(1.6) | |
| Pen needle was bent. Unable to use. | | 1(1.6) |
| The device did not accept some of the strips, it was not possible to measure. | 1(1.6) | |
| The problem with glucometer strips. The device did not accept some of the strips, it was not possible to measure. | 1(1.6) | |
| **Treatment Period Not Specified** | | |
| Humalog pen plunger pulled out of stopper and would not go back in | 1 (1.6) | |

Abbreviations: N = total arm population; n = number of individual patients
Source: Table generated using ADXP dataset provided by Applicant

Given the above findings, the device safety results from studies MYL-GAI-3001 and MYL-GAI-3002 were also reviewed.

In study MYL-GAI-3001, 18 (6.4%) patients in the MYL-1501D arm and 13 (4.7%) patients in the U.S.-Lantus arm reported a device complaint that lead to a dosing error or no dose delivered. 2 (0.4%) patients in the MYL-1501D arm experienced a device related issue that resulted in a TEAE. One patient experienced hyperglycemia as a result of a basal insulin pen malfunction. This was graded as mild. Another patient experienced a contusion to the abdomen that was due to the study drug and pen/needle.

In study MYL-GAI-3002, 9 (3.3%) patients in the MYL-1501D arm and 5 (1.8%) patients in the U.S.-Lantus arm reported device complaints that lead to dosing errors or non-delivery of doses. 1 (0.4%) patient in the MYL-1501D arm experienced a non-serious TEAE graded as mild of injection site swelling in the abdomen. The Investigator considered this TEAE related to the study drug and pen/needle.

In the overall MYL-1501D development program, there were numerically slightly more device complaints reported with use of the MYL-1501D pen device than the U.S.-Lantus pen device. However, the reports were infrequent in both arms and not associated with clinically significant adverse events or diminished efficacy. That is, the small numeric imbalance observed in device complaints did not result in differences in clinical efficacy or safety between MYL-1501D and U.S.-Lantus. As discussed in **Section 2.2**, the FDA review of MYL-GAI-3001 and MYL-GAI-3002 concluded that MYL-1501D was non-inferior to U.S.-Lantus for the primary endpoint of mean change in HbA1c from baseline to week 24 in both phase 3 studies. The review also concluded the safety of MYL-1501D was consistent with the observed safety profile of U.S.-Lantus.

The results from studies MYL-GAI-3001, MYL-GAI-3002, and MYL-1501D-3003 do not suggest a difference in the rate of device malfunctions between the MYL-1501D and U.S.-Lantus pen such that would preclude a determination of biosimilarity or interchangeability of the MYL-1501D 3 mL prefilled pen and the U.S.-Lantus 3 mL prefilled pen.

**Immunogenicity Analyses**

The Applicant assessed immunogenicity by collecting anti-drug antibody (ADA) and anti-host cell protein (anti-HCP) data in study patients. The Applicant used two different conventional radioimmunoprecipitation assays to assess ADAs. They used two assays on account of the potential for structural differences between MYL-1501D and U.S.-Lantus as each was produced by a different host cell. The assays were identical apart from a unique radiolabeled tracer, one for U.S.-Lantus and the other for MYL-1501D. The assay design used a multi-tier approach including a screening tier, confirmatory tier, and a characterization tier. All were assessed simultaneously. ADA complexes were measured via gamma counting and expressed as a percentage of bound to total radioactivity (%B/T). The total ADA and insulin cross-reactivity results were reported as percent specific binding (%SB), which is the relative amount of antibody present in the samples..

At baseline, the Applicant's analysis found there was a larger proportion of patients in the switching arm who were positive for ADAs compared to the U.S.-Lantus arm when analyzed using both the MYL-1501D and U.S.-Lantus assay. This remained true throughout the study and is illustrated below in Table 36. However, the Applicant found the differences between the two arms never reached nominal statistical significance. The Applicant's analyses of the number and proportion of patients in each arm with insulin cross reactive antibodies revealed similar results and are illustrated in Table 37.

**Table 36. Proportion of Patients in Safety Population with Positive Anti-Drug Antibodies**

| | U.S.-Lantus Assay | MYL-1501D Assay |
|---|---|---|

| Time | U.S.-Lantus N = 63 n (%) | Switching arm N = 64 n (%) | p-value | U.S.-Lantus N = 63 n (%) | Switching arm N = 64 n (%) | p-value |
|---|---|---|---|---|---|---|
| Baseline | 42 (66.7) | 47 (73.4) | .831 | 41 (65.1) | 48 (75.0) | .410 |
| Week 2 | 48 (76.2) | 45 (70.3) | .421 | 42 (66.7) | 44 (68.8) | >.999 |
| Week 4 | 43 (68.3) | 50 (78.1) | .234 | 42 (66.7) | 48 (75.0) | .333 |
| Week 8 | 43 (68.3) | 49 (76.6) | .326 | 42 (66.7) | 44 (68.8) | .851 |
| Week 12 | 43 (68.3) | 46 (71.9) | .696 | 40 (63.5) | 47 (73.4) | .256 |
| Week 14 | 44 (69.8) | 49 (76.6) | .545 | 41 (65.1) | 43 (67.2) | >.999 |
| Week 16 | 45 (71.4) | 41 (64.1) | .552 | 42 (66.7) | 42 (65.6) | >.999 |
| Week 20 | 43 (68.3) | 48 (75.0) | .553 | 42 (66.7) | 48 (75.0) | .432 |
| Week 24 | 42 (66.7) | 44 (68.8) | .846 | 39 (61.9) | 46 (71.9) | .246 |
| Week 26 | 41 (65.1) | 46 (71.9) | >.999 | 34 (54.0) | 44 (68.8) | .322 |
| Week 28 | 37 (58.7) | 47 (73.4) | .220 | 35 (55.6) | 43 (67.2) | .433 |
| Week 32 | 33 (52.4) | 45 (70.3) | .082 | 33 (52.4) | 41 (64.1) | .343 |
| Week 36 | 35 (55.6) | 46 (71.9) | .116 | 34 (54.0) | 45 (70.3) | .120 |

Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003 Study, Table 12-7

**Table 37. Proportion of Patients in Safety Population with Positive Insulin Cross Reactive Antibodies**

| | U.S.-Lantus Assay | | | MYL-1501D Assay | | |
|---|---|---|---|---|---|---|
| Baseline | U.S.-Lantus N = 63 n (%) | Switching arm N = 64 n (%) | p-value | U.S.-Lantus N = 63 n (%) | Switching arm N = 64 n (%) | p-value |
| Baseline | 40 (63.5) | 46 (71.9) | .542 | 42 (66.7) | 47 (73.4) | .681 |
| Week 2 | 41 (65.1) | 45 (70.3) | .703 | 44 (69.8) | 47 (73.4) | .843 |
| Week 4 | 42 (66.7) | 45 (70.3) | .705 | 43 (68.3) | 48 (75.0) | .436 |
| Week 8 | 41 (65.1) | 49 (76.6) | .175 | 43 (68.3) | 46 (71.9) | .701 |
| Week 12 | 42 (66.7) | 48 (75.0) | .324 | 41 (65.1) | 45 (70.3) | .573 |
| Week 14 | 45 (71.4) | 45 (70.3) | .845 | 40 (63.5) | 46 (71.9) | .445 |
| Week 16 | 42 (66.7) | 43 (67.2) | .843 | 42 (66.7) | 44 (68.8) | .689 |
| Week 20 | 41 (65.1) | 49 (76.6) | .238 | 39 (61.9) | 48 (75.0) | .178 |
| Week 24 | 41 (65.1) | 44 (68.8) | .699 | 39 (61.9) | 46 (71.9) | .246 |
| Week 26 | 37 (58.7) | 44 (68.8) | .686 | 36 (57.1) | 44 (68.8) | .547 |
| Week 28 | 37 (58.7) | 48 (75.0) | .149 | 37 (58.7) | 42 (65.6) | .844 |
| Week 32 | 35 (55.6) | 43 (67.2) | .334 | 33 (52.4) | 41 (64.1) | .343 |
| Week 36 | 36 (57.1) | 43 (67.2) | .438 | 35 (55.6) | 43 (67.2) | .334 |

Source: Adapted from the Applicant's Clinical Study Report for MYL-1501D-3003 Study, Table 12-6

The Applicant evaluated the mean percent of drug specific ADA bound to total radioactivity (%B/T) for each treatment arm using both assays. At all time points, the drug specific ADA %B/T was close to zero for both arms using both assays. The

Applicant concluded that this indicates that the ADA arising from either drug was cross reactive with the other product.

The Applicant found there were no nominally statistically significant differences between treatment arms for change from baseline in mean total insulin antibody %SB at any scheduled visit with the MYL-1501D assay. This was also true for the U.S.-Lantus assay with the exception of week 28 at which time the Applicant found a nominally statistically significant treatment difference in change from baseline of 2.176; (95% CI 0.396, 3.956, p =0.017) between the two treatment arms.

The Applicant found no nominally statistically significant differences between treatment arms for change from baseline in cross-reactive insulin antibody %SB at any scheduled visit with the MYL-1501D assay. This was also true for the U.S.-Lantus assay except for week 28 at which time the Applicant found a nominally statistically significant treatment difference in change from baseline between the two groups of 2.125 (95% CI 0.387, 3.862, p = 0.017).

The Applicant explored the possibility of antibody neutralization effect by identifying patients who met the following criteria:

- > 10% increase in insulin-cross reactive ADAs from baseline for both U.S.-Lantus and MYL-1501D assay
- > 0.2% increase in HbA1c from baseline
- Increase in total insulin doses

Overall, only 4 patients met the above criteria, 1 (1.6%) patient in the switching arm and 3 (4.8%) patients in the U.S.-Lantus arm.

Finally, the Applicant analyzed the proportion of patients in each arm who had positive anti-host cell protein (anti-HCP) antibodies at each treatment visit. At baseline, 59 (92.2%) patients in the switching arm and 60 (95.2%) patients in the U.S.-Lantus arm were positive for anti-HCP antibodies. The proportion of patients with positive anti-HCP antibodies decreased slightly throughout the course of the study in the switching arm and remained relatively stable in the U.S.-Lantus arm. Despite the slight decrease in the switching arm, the proportion of patients with positive anti-HCP antibodies remained similar between both arms and the Applicant found no statistically significant differences at any time.

*Reviewer comment: While rates of ADA detection across study arms were compared in a variety of ways and at a number of timepoints, no specific hypothesis was formally tested. For that reason, the statistical comparisons submitted by the Applicant should be considered to be descriptive rather than inferential. In the context of a large number of comparisons, the occasional finding of nominally statistically significant differences across study arms do not necessarily support a conclusion that a difference exists.*

*Numerical differences in the proportion of patients with positive antibodies were observed across the study arms, both at study baseline and throughout the study. However, a nominally statistically significant difference in the change from baseline across study arms was observed at only one of 12 post-baseline study visits (at which time the Applicant found a difference in change from baseline between the two groups of 2.125 (95% CI 0.387, 3.862, p = 0.017) with the U.S.-Lantus assay). The descriptive statistical data, therefore, do not support a conclusion that the immunogenicity of the two products are different. Moreover, while numeric differences across study arms with regard to proportion of subjects with detectable ADA were observed, the clincal outcomes across study arms were similar. The immunogenicity data do not preclude a demonstration of biosimilarity or interchangeability.*

### 13.5.5. Study MYL-1501D-3003 Schedule of Activities

| | Visits | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | V1 | V2 | V3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13[1] (EOT) | V14[2] (FU) |
| **Extension Study Week** | 0 | 2 | 4 | 8 | 12 | 14 | 16 | 20 | 24 | 26 | 28 | 32 | 36 | 40 |
| **Extension Study Day** | 0 | 14±3 | 28±3 | 56±3 | 84±3 | 98±7 | 112±7 | 140±7 | 168±7 | 182±7 | 196±7 | 224±7 | 252±7 | 280±7 |
| Informed Consent[3] | x | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria Review | x | | | | | | | | | | | | | |
| Previous and current insulin usage history | √ | | | | | | | | | | | | | |
| Dilated Ophthalmoscopy / Retinal photography testing[4] | x | x | x | | | | | | | | | | | |
| Standard-of-care specifics[5] | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Age, Gender, Race | x | | | | | | | | | | | | | |
| Body Weight, Height and BMI[11] | √ | | | | | | | | | | | | x | |
| Pregnancy Test[6] | √ | x | x | x | x | x | x | x | x | x | x | x | x | |
| Medical History and Concomitant Illness | x | | | | | | | | | | | | | |
| Concomitant Medications | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Vitals signs measurement (sitting) | √ | x | x | x | x | x | x | x | x | x | x | x | x | |
| Physical examination | √ | x | | | x | x | | | x | x | | | x | |
| 12-lead ECG (supine) | √ | | | | x | x | | | x | x | | | x | |
| Fresh Randomization with capture of old randomization number[7] | x | | | | | | | | | | | | | |
| Record AEs and SAEs, local and systemic allergic reactions and hypoglycemic events[8] | x | x | x | x | x | x | x | x | x | x | x | x | x | x[12] |
| Record device safety information (disposable needle or pen) | | x | x | x | x | x | x | x | x | x | x | x | x | |
| Fasting Plasma Glucose | √ | | | x | x | | | x | x | | | | x | |
| HbA1c Assay | √ | | | | x | | | | x | | | | x | |
| HIV, HBsAg, and HCVAb | √ | | | | | | | | | | | | | |
| Sampling for hematology, blood chemistry and urinalysis[9] | √ | | | | x | | | | x | | | | x | |
| Fasting lipid profile | √ | | | | x | | | | x | | | | x | |
| Sampling for immunogenicity | √ | x | x | x | x | x | x | x | x | x | x | x | x | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Review 8-point SMBG Profile performed in the week before the visit[10] | √ | x | x | x | x | x | x | x | x | x | x | x | x | |
| Dose review of Mylan's insulin glargine/US-Lantus and insulin lispro and instruction | x | x | x | x | x | x | x | x | x | x | x | x | | |
| Dispense Trial Medication and ancillary supplies | x | | x | x | x | | x | x | x | | x | x | | |
| Drug Accountability and Compliance | | x | x | x | x | x | x | x | x | x | x | x | x | |
| Dispense patient diary | x | x | x | x | x | x | x | x | x | x | x | x | | |
| Review patient diary | | x | x | x | x | x | x | x | x | x | x | x | x | |

1. At the EOT the Investigator will discuss with the patient the prescription medication that the patient should take after the end of the extension study, and provide dosing instructions. (Mylan will not provide any medications from 36 weeks of treatment onwards)
2. Follow-up visit will be a telephone contact.
3. Informed consent should be signed on the Day "0" prior to initiating any study related activities
4. Dilated Ophthalmoscopy / Retinal photography testing should be performed once within one of the visits during the 28 days of enrolment
5. Standard–of-care specifics includes assessment and documentation of the following - Training on self-management of diabetes, lifestyle modification measures (includes maintenance of appropriate body weight, following recommended physical activity, avoidance of smoking and following the recommended diet); and monitoring to prevent complications.
6. Urine pregnancy test will be conducted at specified visits. Results of the pregnancy test should be confirmed as negative before dispensing trial drug(s).
7. The MYL-GAI-3001 randomization number should also be captured during the new randomization along with the new randomization numbers.
8. Hypoglycemia that had occurred before MYL-1501D-3003 week 0 visit will be noted in source document and will be used for comparisons. Ongoing adverse events from MYL-GAI-3001 will be recorded as adverse events.
9. A routine urine dipstick will be performed by the site. A urinalysis by microscopic urinalysis may be performed by the central lab if the dipstick result is abnormal, and if requested by the Investigator.
10. The 8-point SMBG profile measurement needs to be done by the patient at home on any 3 days (of which 2 days should be consecutive) in the week of the visit (i.e. during the 7 days before the day of the visit).
11. Only body weight will be measured at EOT visit. Height at V1 of MYL-GAI-3001 will be used to calculate BMI.
12. Allergic reactions, AEs and SAEs will be captured.

'√' represents information already collected in the MYL-GAI-3001 trial. The same information should be used in this extension study.

'x' represents new information to be collected in the extension study.

AE: adverse event; BMI: body mass index; ECG: electrocardiogram; EOT: end of treatment; HbA1c: glycosylated hemoglobin; HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C virus antibody; HIV: Human Immunodeficiency Virus; SAE: serious adverse event; SMBG: self-monitored blood glucose.

Hematology panel will include hemoglobin, hematocrit, white blood cell count with differentials, red blood cell count with indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration) and platelet count.

Blood chemistry panel will include blood urea / BUN, serum creatinine, creatinine kinase, uric acid, serum bilirubin (total and direct), total protein, serum albumin, ALT, AST, alkaline phosphatase, LDH, lipase, sodium, potassium, calcium, magnesium, chloride, and bicarbonate.

For the urinalysis a routine urine dip will be performed by the site, using supplies provided by the central laboratory. This will include assessment of specific gravity, pH, and semiquantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood. If the investigators want to do detailed urine testing, the site will send a urine sample to the central laboratory for microscopic evaluation. Microscopic examination will include WBC, RBC, casts, cast type, crystals, epithelial cells, renal cells, mucus threads, bacteria, yeast, and Trichomonas)

Physical examination activities will include the following assessments: general appearance, head, ears, eyes, nose and throat (including thyroid), skin, respiratory system, cardiovascular system, abdomen,

lymph nodes, musculoskeletal system, gastrointestinal system (including mouth) and neurological system; and a diabetic foot examination
Source: Adapted from MYL-1501D-3003 Clinical Study Protocol

# BLA 761201 Semglee (insulin glargine-yfgn) injection

## Signatures

| Discipline and Title or Role | Reviewer Name | Office/Division | Sections Authored/Approved |
|---|---|---|---|
| Nonclinical Reviewer | Patricia Brundage | OCHEN/DPTCHEN | 4, 13.3 |
| | Signature: Patricia Brundage -S Digitally signed by Patricia Brundage -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000221055, cn=Patricia Brundage -S Date: 2021.07.28 11:18:30 -04'00' | | |
| Nonclinical Team Leader | Federica Basso | OCHEN/DPTCHEN | 4, 13.3 |
| | Signature: Federica Basso -S Digitally signed by Federica Basso -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Federica Basso -S, 0.9.2342.19200300.100.1.1=0011076316 Date: 2021.07.28 12:40:58 -04'00' | | |
| Clinical Pharmacology Reviewer | Lin Zhou | OCP/DCEP | 5, 13.4 |
| | Signature: Lin Zhou -S Digitally signed by Lin Zhou -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lin Zhou -S, 0.9.2342.19200300.100.1.1=2000423233 Date: 2021.07.28 11:40:17 -04'00' | | |
| Clinical Pharmacology Team Leader | Manoj Khurana | OCP/DCEP | 5, 13.4 |
| | Signature: Manoj Khurana -S Digitally signed by Manoj Khurana -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Manoj Khurana -S, 0.9.2342.19200300.100.1.1=1300421048 Date: 2021.07.28 11:44:37 -04'00' | | |
| Clinical Reviewer | Ann Miller | OCHEN/DDLO | 2, 6, 7, 8, 10, 13.2, 13.5 |
| | Signature: Ann Miller Digitally signed by Ann Miller DN: cn=Ann Miller, o, ou, email=ann.miller@fda.hhs.gov, c=US Date: 2021.07.28 11:25:48 -04'00' | | |

| | | | |
|---|---|---|---|
| Clinical Statistics Reviewer | Roberto Crackel | OB/DBII | 6 |
| | Signature: Roberto C. Crackel -S<br>Digitally signed by Roberto C. Crackel -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001729661, cn=Roberto C. Crackel -S<br>Date: 2021.07.28 11:14:34 -04'00' | | |
| Clinical Statistics Team Leader | Yun Wang | OB/DBII | 6 |
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| Clinical Team Leader/ Cross-Discipline Team Leader/ Signatory Authority | Patrick Archdeacon | OCHEN/DDLO | All |
| | Signature: Patrick Archdeacon -S<br>Digitally signed by Patrick Archdeacon -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000254556, cn=Patrick Archdeacon -S<br>Date: 2021.07.28 13:08:56 -04'00' | | |

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/s/

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PATRICK ARCHDEACON
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