CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210605Orig1s000

CLINICAL REVIEW(S)

CDTL Review and
Division Summary Memo for Regulatory Action

Date	
From	Patrick Archdeacon, M.D.
NDA #	210605
Applicant	Mylan
Date of Submission Receipt	February 28, 2019
PDUFA Goal Date	August 28, 2019
Established (USAN) names	Insulin glargine injection
Trade names	Semglee
Dosage forms / Strength	Solution for sc injection / 100 units/mL
Proposed Indication	To improve glycemic control in adults and children with type 1 diabetes mellitus and adults with type 2 diabetes mellitus
Recommended Action	Complete Response

1. Introduction

This document contains the 'Summary Basis for Regulatory Action' memo for the resubmission of NDA 210605 for Mylan's proposed insulin glargine (also known as MYL-1501D, proposed proprietary name: Semglee) disposable pen presentation and vial presentation. Mylan (hereafter referred to as the Applicant) submitted the NDA through the 505(b)(2) regulatory pathway. FDA issued a Complete Response Letter (CRL) to the original submission of NDA 210605.

Each proposed presentation in this NDA relies, in part, on FDA's finding of safety and effectiveness for Lantus and Lantus Solostar (NDA 21081; insulin glargine injection), which are collectively described as "Lantus" in this review. Lantus was initially approved on April 20, 2000. Lantus is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. NDA 210605 describes the use of MYL-1501D in combination with the (b) (4) disposable pen; this presentation of MYL-1501D is therefore a combination product. NDA 210605 also includes a presentation of MYL-1501D in a 10 mL vial.

The resubmission includes responses to the deficiencies (including clinical-related major deficiencies, product quality-related major deficiencies, and human factors-related major deficiencies) cited in the CRL issued to the original NDA submission. The individual discipline reviewers concluded (and I concur) that the resubmission adequately addressed the clinical-related major deficiencies and the human factors-related major deficiencies. However, persistent major deficiencies related to product quality preclude approval of NDA 210605 at this time.

The reader is referred to the individual discipline reviews and to the reviews of the original NDA submission for a more comprehensive discussion of the MYL-1501D development program.

This memo references the following documents/sources:

Subject	Author	Date
Clinical Efficacy and Safety Review (DMEP)	Sonia Doi	August 27, 2019
Statistical (DBII) review	Anna Ketterman	July 15, 2019
CDRH review	Rong Guo	May 28, 2019
Clinical Pharmacology review	Jing Niu	July 25, 2019
Clinical Pharmacology review addendum	Jing Niu	August 22, 2019
OBP Immunogenicity review	Fred Mills	July 24, 2019
DMEPA Human Factors and	Jason Flint and Ariane Conrad	August 15, 2019

Labeling review		
DMEPA revised label review	Ariane Conrad	August 21, 2019
DMEPA Proprietary Name Review	Ariane Conrad	April 19, 2019
OPDP review	Ankur Kalola	August 19, 2019
Patient Labeling Team	Ankur Kalola, Aman Sarai	August 20, 2019
OPQ review	Muthu Ramaswamy; Joseph Leginus; Jennifer Patro; Vidya Pai; Leeza Rahimi	August 22, 2019
DMEP: Division of Metabolism and Endocrinology Products; DBII: Division of Biometrics II; CDRH: Center for Devices and Radiological Health; OBP: Office of Biotechnology Products; DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion; DNDBE: Division of New Drug Bioequivalence Evaluation; OPQ: Office of Pharmaceutical Quality		

2. Background

NDA 210605 was originally submitted on April 27, 2017. FDA refused to file the original submission because the drug product (MYL-1501D Process V) used in the submitted PK/PD clamp studies and the pivotal phase 3 trials was manufactured using a different process than the drug product intended to be marketed (MYL-1501D Process VI). The Applicant stated that they adopted Process VI in response to advice from the European Medicines Agency (EMA) to reduce impurities in the drug substance: the use of Process VI reduces (b) (4) of insulin glargine compared to Process V. However, at the time of the original submission, the Applicant did not include data that adequately bridged MYL-1501D Process V and MYL-1501D Process VI. This deficiency was identified prior to the original NDA submission and was communicated to the Applicant both prior to the original NDA submission and as part of a Refuse-to-File decision.

On August 15, 2017, a Type A meeting was held to discuss the Refuse-to-File decision. At that meeting, the Applicant was informed that they could request that the application be Filed Over Protest and that the Agency would be obliged to review the application. At that meeting, the Applicant was also advised to conduct an 18-week clinical study to support a bridge between the Process V and Process VI drug products. On August 31, 2017, the Applicant requested that its NDA be Filed over Protest. Accordingly, the NDA was filed over protest on September 15, 2017 (60 days after the date on which the Applicant requested the meeting described above) and FDA completed the review of the original NDA submission. On September 19, 2017, the Applicant submitted a clinical protocol to IND 105279 for an 18-week clinical bridging study.

FDA issued a CRL on May 17, 2018 in response to the original NDA submission. The deficiencies cited in the CRL included, but were not limited to, the absence of adequate bridging data to establish that the clinical trial data generated with MYL-1501D Process V are relevant to MYL-1501D Process VI and can be used to support a determination that the proposed to-be-marketed product (i.e., MYL-1501D Process VI) is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus.

Other deficiencies cited were:

- The absence of bridging data necessary for approval of the vial presentation of MYL-1501D.
- Objectionable findings during inspection of the manufacturing facility (Biocon Sdn. Bhd. FEI#3011248248).
- Lack of method suitability data for endotoxin, sterility, and antimicrobial effectiveness testing (AET).
- Lack of AET data supporting the product expiry from stability.
- Human factors-related major deficiencies.

The Applicant resubmitted NDA 210605 on February 28, 2019. The resubmission package included data from two new euglycemic clamp PK/PD studies (MYL-1501D-1003: comparing MYL-1501D Process V, MYL-1501D Process VI, and US-Lantus; MYL-1501D-1004: comparing cartridge and vial formulations of MYL-1501D Process VI) and a new efficacy and safety study conducted in patients with type 1 diabetes mellitus (MYL-1501D-3004: comparing MYL-1501D Process V and MYL-1501D Process VI). MYL-1501D-3004 was conducted to provide adequate bridging data to establish that the clinical trial data generated with MYL-1501D Process V are relevant to MYL-1501D Process VI. MYL-1501D-1004 was conducted to bridge the prefilled pen and vial presentations. MYL-1501D-1003 did not address any deficiencies cited in the CRL, but confirmed the conclusions based on the review of MYL-1501D-1001. The resubmission also included responses to the other deficiencies cited in the CRL, including corrective and prevention actions (CAPA) execution updates to address the inspection findings, AET method validation, additional CMC data, the results of an additional human factors pediatric validation study, and an additional differentiation study.

3. CMC/Device

The Office of Pharmaceutical Quality (OPQ) performed the overall quality/CMC review for both the original submission, as well as the resubmission, of NDA 210605. At the time of the original submission, the drug substance, drug product, and manufacturing process reviews recommended approval. However, OPQ recommended a complete response for the original submission due to issues related to the drug substance and drug product manufacturing facility (Biocon Sdn. Bhd., FEI#3011248248) as well as microbiology issues; Biocon (Mylan's development partner) is described as having commissioned this new drug substance and drug product manufacturing site (L2) to meet anticipated global commercial demand.

OPQ continues to recommend approval based on the drug substance, drug product, and process reviews. Further, OPQ has determined based on its reviews of the resubmission that the microbiology issues have been resolved. However, the pre-approval inspection of the facility between June 24, 2019 and July 5, 2019 again resulted in a "withhold recommendation" from Office of Regulatory Affairs (ORA) due to objectionable conditions observed. To correct the deficiencies, Biocon has committed to completing several corrective actions, outlined in the Process/Facility review. Successful completion and implementation of the corrective actions and quality management system improvements are required before the facility can be considered acceptable. I concur with this recommendation.

Manufacturing Process

Dr. Vidya Pai reviewed the manufacturing processes for both the cartridge/pre-filled pen presentation and the vial presentation of the MYL-1501D drug product. The manufacturing processes for both presentations involves (b) (4) (b) (4). Dr. Pai concluded, and I concur, that the NDA was acceptable from the perspective of the manufacturing processes.

The pivotal clinical studies were conducted with Process V drug product manufactured at the Bangalore, India site (L1). The proposed commercial site (L2) is the Malaysia facility.

Facility Compliance

Dr. Vidya Pai also reviewed the facility compliance information for drug product and drug substance manufacturing facilities for the site in Malaysia (FEI#3011248248). The pre-approval inspection of the L2 site between June 24, 2019 and July 5, 2019 resulted in a "withhold recommendation" from Office of Regulatory Affairs (ORA) due to objectionable conditions observed. As noted in Dr. Pai's review, that inspection took place in the context of a "withhold recommendation" for this same site from the previous review cycle; the unfavorable findings at that time included (b) (4) (b) (4).

The current inspection resulted in the issuance of a 12-item Form FDA 483. Several of the items cited on the Form 483 were repeat observations from the previous inspection. (b) (4) (b) (4) (b) (4) Please see the Form FDA 483 for additional details. The establishment inspection report (EIR) and the review of the firm's responses to the results of the inspection supported the conclusion of the inspection report: the site has not demonstrated that it can reliably manufacture product at commercial scale. To correct the deficiencies, Biocon has committed to (b) (4) (b) (4) (b) (4). Successful completion and implementation of the corrective actions is required before the facility can be considered acceptable. Biocon's timeline for the proposed improvement initiatives extends into December 2019. As Biocon's responses do not adequately address all the identified concerns at this time, Dr. Pai concluded that the Biocon Sdn Bhd facility is not acceptable to support NDA 210605 for non-sterile drug substance and sterile drug product manufacturing (b) (4).

Drug Substance

Dr. Joseph Leginus reviewed the CMC information provided for MYL-1501D drug substance (DS) and concluded that the information in the application demonstrated consistent production of insulin glargine achieving a well-defined quality. There were no deficiencies associated with the drug substance cited in the May 17, 2018 CRL. Updates to the drug substance information received in the resubmission of the NDA included a revision of an in-process control limit for an impurity, calculation of impurity levels using HPLC and SEC methods, and additional stability data. The new in-process specification (b) (4) the limit of RP-HPLC-II for the impurity (b) (4); this was justified by demonstrating that the (b) (4) specification limit did not impact the impurity profile of 5 lots produced with the new limit. The Applicant addressed an Additional Comment in the CRL to revise the HPLC and SEC impurity methods; Dr. Leginus concluded the revisions were adequate. Finally, Dr. Leginus concluded that the long-term stability studies demonstrated that the insulin glargine is chemically and physically stable under the conditions tested. Overall, Dr. Leginus concluded (and I concur) that the information on the drug substance is adequate to support approval.

Drug Product

Dr. Muthu Ramaswamy reviewed the drug product for both the 10mL multi-dose vial presentation and the 3mL disposable prefilled pen presentation for the resubmission of NDA 210605. Dr. Joanne Wang had previously reviewed the batch formula, manufacturing process description, process development, and process validation information for the drug product for the original NDA submission and had found the application approvable.

Per FDA request, the Applicant provided additional information in the NDA resubmission on the drug product batches used in clinical studies MYL-1501D-3004, MYL-1501D-1003, and MYL-1501D-1004. The Applicant also provided end of expiry impurity profile and potency comparisons for the Mylan drug product and for Lantus to address deficiencies identified in the CRL. The submission included data generated using the USP method and also a Mylan in-house method to measure impurities. Dr. Ramaswamy concluded that the accelerated stability results indicated that aged Mylan batches degraded faster than Lantus batches. Real-time and accelerated stability results, however, did not indicate any difference in potency between the two. Dr. Ramaswamy found that the available stability data support a shelf-life of 24 months for the cartridge/prefilled pens and the vials when stored at 5ºC ± 3ºC and 28 day in-use period for storage at up to 30ºC. Dr. Ramaswamy agreed that the Applicant's previously discussed proposed specification revision for individual impurity and revised methods for measuring impurities (see *Drug Substance* above) are acceptable. Dr. Ramaswamy concluded that overall the analytic similarity assessment demonstrates that the major impurities present in the MYL-1501D drug product are generally the same as the Lantus product and that no further impurity profile comparisons are needed.

Microbiology

Dr. Jennifer Patro reviewed the microbiological controls associated with the drug product manufacturing process. The key outstanding issues from the last review cycle were the lack of AET data and lack of method suitability data for endotoxin, sterility, and AET. Based on the

additional information in the resubmitted NDA, Dr Patro concluded (and I concur) that the submitted AET method and results and the endotoxin and sterility methods are adequate. The Applicant committed to provide additional AET data extending to the 36-month time point (b) (4).

Immunogenicity

Dr. Frederick Mills reviewed the immunogenicity data and the immunogenicity assays for both the original submission and also the resubmission of NDA 210605. The immunogenicity data generated included ADA, anti-insulin, and HCP antibody data. He concluded that the immunogenicity assays are suitable for their intended purpose. He also concluded, and I concur, that the additional data support the conclusion that there are no important immunogenicity differences in subjects treated with MYL-1501D or Lantus.

The original submission compared Lantus and MYL-1501D Process V in the clinical trials of safety and efficacy. The OBP review for those data concluded there were no significant immunogenicity differences between Lantus and MYL-1501D Process V. The resubmission included new immunogenicity data from Study MYL-1501D-3004, which compared Process V MYL-1501D to Process VI MYL-1501D (see Section 6 below for additional details on MYL-1501D-3004). The ADA screening and confirmatory assays used RadioImmuno Precipitation Assay (RIPA) methodology. The % binding (%B/T) is calculated as the ratio of the precipitated counts to total gamma counts for the uninhibited tube (RIPA assay buffer only) as well as for tubes inhibited with MYL-1501D, Lantus, or regular human insulin. For this Study, the Applicant considered subjects who were ADA negative at baseline and positive at any time during the study OR who were ADA positive at baseline and experienced an increase of ≥ 30% SB at any time during the study as having a treatment emergent antibody response (TEAR). No significant differences were observed between the immunogenic responses to MYL-1501D Process V and MYL-1501D Process VI (see Table 1).

Table 1: Anti-Drug Antibody Response in MYL-GAI-3004

	MIG assay	
	MYL-1501D Process VI (N=110) n (%)	**MYL-1501D Process V (N=108) n (%)**
Cross Reactive ADA	29 (26.4%)	28 (25.9%)
Difference	0.44%	
90% CI	(-9.35%, 10.23%)	
P value	0.941	
Total ADA	30 (27.3%)	32 (29.6%)
Difference	-2.35%	
90% CI	(-12.41%, 7.69%)	
P value	0.700	

Center for Devices and Radiologic Health (CDRH)

Dr. Rong Guo recommended approval of the device constituent of the combination product, as documented in the previous review from Dr. Guo uploaded to DARRTS on March 27, 2018, in response to the original submission of NDA 210605. The resubmission included no changes to the pen injector, but did add Biocon Sdn. Bhd. Facility (FEI#3011248248) as a new facility for pen assembly. For that reason, the facility inspection also included a medical device quality system inspection.

4. Nonclinical Pharmacology/Toxicology

The NDA resubmission includes no new nonclinical data. In the original submission, Dr. Arulasanam Thilagar reviewed the nonclinical data submitted to the NDA. He found that the pharmacology/toxicology data supports a determination that NDA is approvable; I concur with his recommendation.

The Applicant conducted in vitro pharmacology assays, in vivo pharmacodynamic (PD) and pharmacokinetic (PK) studies, along with in vitro insulin receptor (IR), insulin-like growth factor-1 receptor (IGF-IR) binding studies, cell-based receptor-dependent metabolism and mitogenicity studies, and a repeat-dose rat toxicity study to compare MYL-1501D and US-approved Lantus. The Applicant conducted many nonclinical studies with MYL-1501D Process V drug substance in addition to the head-to-head nonclinical in vitro and in vivo studies with MYL-1501D Process VI and US-approved Lantus that were found by Dr. Thilagar to provide adequate support to the NDA submission. The review of the submitted studies evaluated all the in vitro and in vivo toxicology studies comparing MYL-1501D Process VI and US-approved Lantus. Dr Thilagar found that those pharmacology/toxicology data support the similarity of MYL-1501D Process VI and US-approved Lantus. Dr. Thilagar did not review all of the nonclinical studies that used formulations different from the Process VI MYL-1501D formulation or performed with comparators other than US-approved Lantus. Please see Dr. Thilagar's review of the original NDA, dated April 10, 2018, for details.

The toxicology studies bridging MYL-1501D Process VI and Lantus support an abbreviated non-clinical development program and provide an adequate scientific justification for reliance on FDA's finding of safety for Lantus as reflected in product labeling that describes, among other things, reproduction and early development, carcinogenicity, and chronic toxicology studies.

5. Clinical Pharmacology/Biopharmaceutics

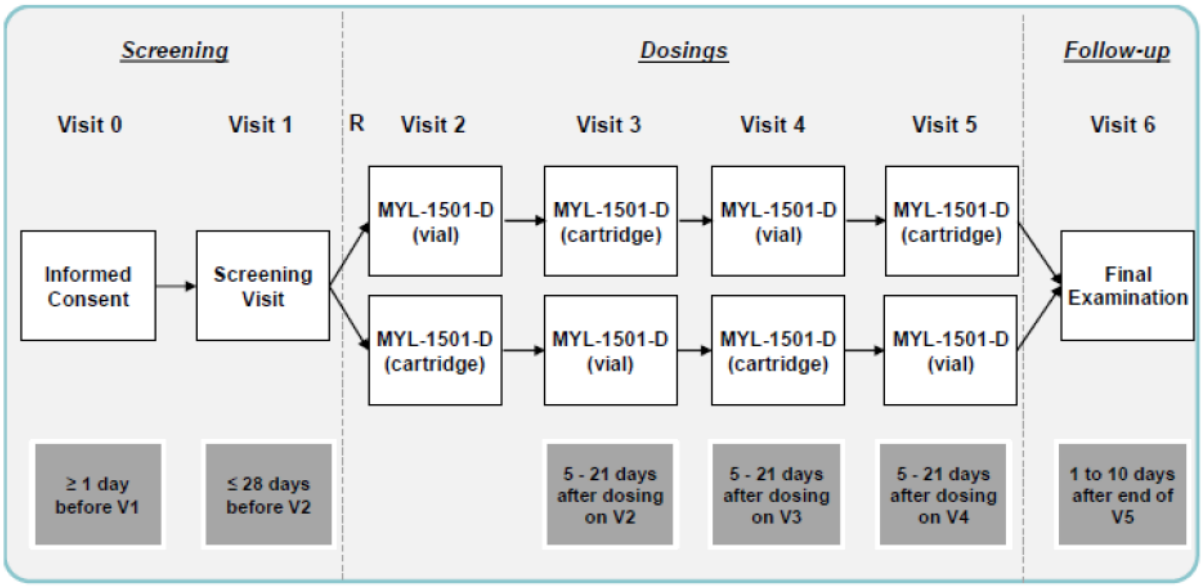
Dr. Jing Niu evaluated the clinical pharmacology data for both the original submission and the resubmission of NDA 210605. As noted in the CRL, the original submission did not include bridging data necessary for approval of the vial presentation. The original submission did include two PK/PD studies (MYL-1501D-1001 and GLARGCT100111). The resubmission included two new PK/PD studies: MYL-1501D-1003 and MYL-1501D-1004. Dr Niu concluded that MYL-1501D-1004 established PK/PD comparability between MYL-1501D Process VI vial presentation (with polysorbate) and MYL-1501D Process VI cartridge/pre-

filled pen presentation (without polysorbate). She also concluded that the results of MYL-1501D-1003 were consistent with the results of MYL-1501D-1001 (the pivotal clamp study of the original submission). I concur with Dr. Niu's conclusions. See Dr. Niu's review for additional details.

Study MYL-1501-1004 was a pivotal study for the resubmission of NDA 210605 because the pivotal clinical studies (MYL-GAI-3001, MYL-GAI-3002, and MYL-GAI-3004) were all conducted using the cartridge/pre-filled pen presentation of MYL-1501D. The formulations of the vial and cartridge/pre-filled pen presentations, however, are different: the formulation of MYL-1501D used in the vial includes polysorbate-20 (b) (4). Approval of the vial presentation therefore requires an adequate bridge between the vial and cartridge/pre-filled pen presentations.

Study MYL-1501D-1004 was a Phase 1, two-center, randomized, double-blind, 4-way crossover trial comparing single doses of MYL-1501D Process VI vial presentation with MYL-1501D Process VI in cartridge presentation. A total of 48 subjects were randomized to one of two treatment sequences.

Figure 1: Trial Design for Study MYL-1501D-1004



Source: FDA Clinical Pharmacology Review

As described by Dr. Niu and shown in Table 2, the equivalence criteria (90% CI of the ratio test/reference within 80-125%) were met for both primary PK parameters (AUC0-24h and Cmax of insulin glargine metabolite M1).

Table 2: Treatment comparisons of PK parameters in Study MYL-1501D-1004

Parameter	Comparison	N Obs Vial/Cartridge	Geometric LS-mean ratio %	90% CI
AUC_{0-24h}	MYL-1501D vial vs. cartridge	70/72	97.82	(90.33; 105.94)
C_{max}		70/72	97.80	(91.55; 104.48)
AUC_{0-12h}		70/73	99.57	(90.26; 109.84)
AUC_{12-24h}		70/72	97.31	(88.95; 106.46)
AUC_{0-inf}		43/42	104.91	(95.47; 115.28)

Source: FDA Clinical Pharmacology Review

Similarly, as shown in Table 3, the equivalence criteria (90% CI of the ratio test/reference within 80-125%) were met for both primary PD parameters (AUCGIR0-24h and GIRmax) in MYL-1501-1004.

Table 3: Treatment comparisons of PD parameters in Study MYL-1501D-1004

Parameter	Comparison	N Obs Vial/Cartridge	Geometric LS-mean ratio %	90% CI
$AUC_{GIR0-24h}$	MYL-1501D vial vs. cartridge	90/90	99.98	(93.96; 106.39)
GIR_{max}		90/90	99.54	(93.52; 105.95)
$AUC_{GIR0-12h}$		90/90	102.63	(95.93; 109.79)
$AUC_{GIR12-24h}$		90/90	96.93	(89.82; 104.60)

Source: FDA Clinical Pharmacology Review

Despite the results shown in Table 2 and Table 3, the FDA clinical pharmacology reviewers (Dr. Niu and her team leader, Dr. Manoj Khurana) discussed the acceptability of Study MYL-1501D-1004 with the Office of Clinical Pharmacology (OCP) Senior Leadership Team due to an unusually high number of un-usable PK profiles. The root cause of the un-usable PK profiles is likely that the lower level of quantitation for assay used to measure the M1 metabolite was 0.2 ng/mL. OCP determined that the exclusion of unusable PK profiles was in accordance with the Statistical Analysis Plan (SAP). OCP also noted that after the profiles were excluded, the BE criteria were met, indicating that the study was overpowered. OCP further noted that replicate crossover PK/PD clamp studies typically enroll 24 subjects, compared to available and evaluable PK data from 40 subjects in MYL-1501D-1004. I concur with the rationale provided by OCP.

The Applicant also submitted the results of Study MYL-1501D-1003, a Phase 1, randomized, double-blind, single-does, three-treatment (MYL-1501D Process V, MYL-1501D Process VI, and US-Lantus), six period, six sequence, fully replicated, euglycemic glucose clamp study in healthy subjects, even though the study did not address any deficiencies cited in the CRL. Dr. Niu treated MYL-1501D-1003 as an additional pivotal study because it studied the to-be-marketed product. Dr. Niu concluded that the results of Study MYL-1501D-1003 confirmed the conclusions based on Study MYL-1501-1001 submitted with original NDA 210605: in Study MYL-1501D-1003, the equivalence criteria (90% CI of the ratio test/reference within 80-125%) were met for the primary PK and PD parameters for the three-way comparison of

MYL-1501D Process V, MYL-1501D Process VI, and US-Lantus, demonstrating PK/PD similarity across all three products. It is important to note that while MYL-1501D-1001 and MYL-1501D-1003 established PK/PD similarity between MYL-1501D Process V and MYL-1501D Process VI, these clamp studies were not able to provide the requested scientific bridge between the Process V and Process VI drug products because they did not include an assessment of immunogenicity associated with the drug products.

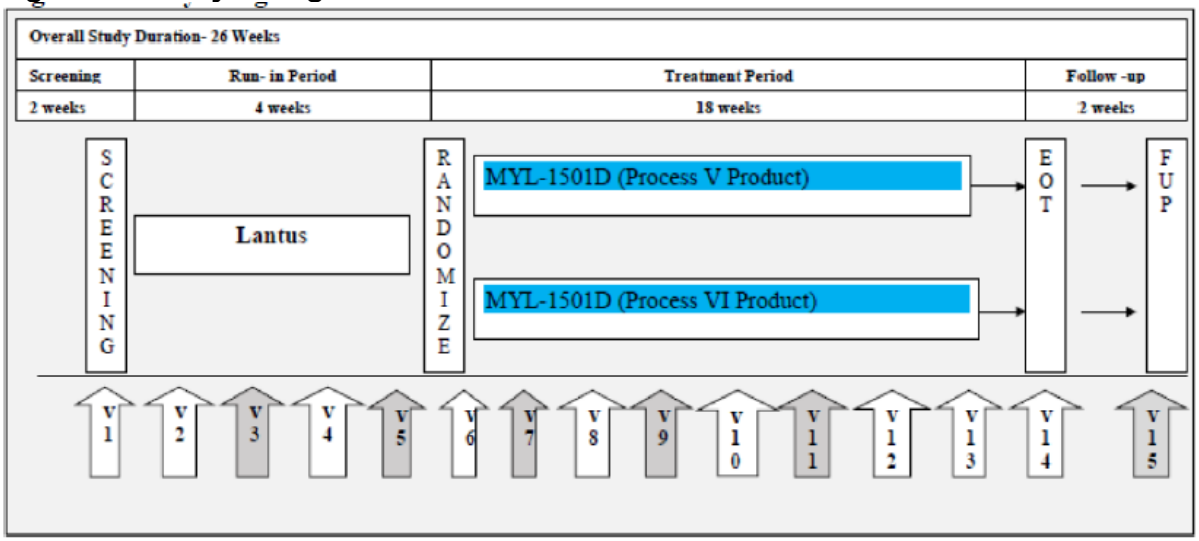
6. Clinical/Statistical- Efficacy

In the original NDA submission, Dr. Anna Ketterman and Dr. Mitra Rauschecker evaluated the clinical trial data from MYL-GAI-3001 (patients with T1D) and MYL-GAI-3002 (patients with T2D). Those trials established the non-inferiority of MYL-1501D Process V to Lantus.

Dr. Anna Ketterman and Dr. Sonia Doi evaluated the new clinical trial data from MYL-1501D-3004 submitted to the NDA. Both Dr. Ketterman and Dr. Doi concluded, and I concur, that the submitted data demonstrate the non-inferiority of MYL-1501D Process VI to MYL-1501D Process V, based on change in HbA1c from baseline to Week 18 when administered in combination with mealtime insulin lispro. The study also evaluated immunogenicity observed with the two drug products. The evaluation of immunogenicity is discussed by Dr. Mills in Section 3 and Dr. Doi in Section 7. Please see the reviews of Drs. Ketterman, Mills, and Doi for additional details.

Study MYL-1501D-3004 was a multicenter, randomized, double-blind, parallel assignment T1DM trial that compared MYL-1501D Process V and MYL-1501D Process VI. After a 2 week screening period and a 4 week run-in period, patients received treatment with the assigned drug product for 18 weeks. There was a safety follow up visit at 2 weeks after the end of the treatment period (see Figure 2). The trial randomized 219 patients to either MYL-1501D Process V or MYL-1501D Process VI.

Figure 2: Study Design MYL-1501D-3004



Source: FDA Statistical Review

The primary efficacy endpoint of MYL-1501D-3004 was change in HbA1c at Week 18. Total and basal insulin doses were similar across treatment arms throughout the study. Dr. Ketterman used a return to baseline multiple imputation and ANCOVA analysis to conduct her evaluation (see her review for details). She concluded that change in HbA1c was similar for the MYL-1501D Process V and MYL-1501D Process VI drug products: the upper bound of the 95% confidence interval was 0.1 (see Table 4).

Table 4: Change in HbA1c (%) from Baseline to Week 18 using Return to Baseline Imputation Approach (including post-rescue HbA1c values)

HbA1c	Process VI	Process V
Change in HbA1c (%) at Week-18 from baseline, adjusted mean (95% CI)	0.14(0.05, 0.24)	0.18(0.08, 0.28)
Difference in change (%) between Process VI and V, adjusted mean (95% CI)	-0.04 (-0.18, 0.1)	

Source: FDA Statistical Review

Based on her analysis of the HbA1c data from MYL-1501D-3004, Dr. Ketterman concluded that MYL-1501D Process VI is non-inferior to MYL-1501D Process V. In conjunction with the data from the previous review of MYL-GAI-3001 and MYL-GAI-3002 (which demonstrated the non-inferiority of MYL-1501D Process V to Lantus), Dr. Ketterman concluded that MYL-1501D Process VI is non-inferior to Lantus. Dr. Doi and I concur with the statistical analysis and the efficacy conclusions of Dr. Ketterman regarding MYL-1501D-3004.

7. Safety

Dr. Doi also evaluated MYL-1501D-3004 from the perspective of safety, including immunogenicity. The safety assessments conducted included physical examinations, vital signs, ECGs, laboratory analyses, adverse events, immunogenicity, and hypoglycemia. Overall, Dr. Doi concluded that the safety findings from MYL-1501D-3004 were consistent with the safety finding of the clinical trials included in the original NDA submission and consistent with the known safety profile of Lantus. She also concluded (and I concur) that the data from MYL-1501D-3004 provide sufficient additional clinical safety and efficacy bridging data, including an assessment of immunogenicity, to establish that the efficacy and safety data generated with the Process V drug product is relevant to the Process VI drug product (i.e., the to-be-marketed product) and can be used to support a determination that the proposed to-be-marketed product is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus.

Overall safety

No deaths were observed in MYL-1501-3004. A total of 3 serious adverse events (SAEs) were reported in association with MYL-1501D Process V: they were all events of severe hypoglycemia. A total of 7 SAEs were reported in association with MYL-1501D Process VI: they comprised 4 events of severe hypoglycemia, 1 finger laceration, 1 food allergy, and 1

event of diabetic ketoacidosis. The overall number of patients experiencing AEs and TEAEs and the overall number of AEs and TEAEs were similar across treatment arms.

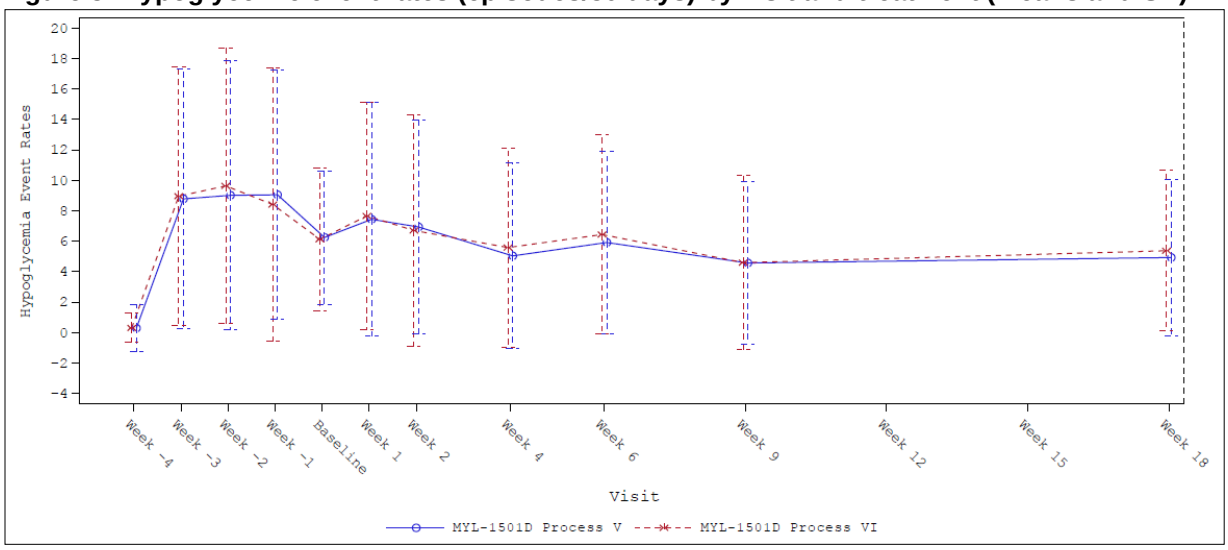
Immunogenicity

Dr. Doi's review of the immunogenicity data drew on the evaluation of OBP and Dr. Mills previously described in Section 3 above. In addition to considering the evaluation of TEAR and other measures of ADAs described by Dr. Mills, Dr. Doi evaluated the data for evidence of an association of immunogenicity with hypersensitivity reactions, injection site reactions, and severe hypoglycemic events: she found no reports of hypersensitivity reactions in either treatment group and no significant differences between groups for the incidence of injection site reactions (no events among patients randomized to MYL-1501D Process V; 1 event among patients randomized to MYL-1501D Process VI) or severe hypoglycemic events (three events among patients randomized to MYL-1501D Process V; 2 events among patients randomized to MYL-1501D Process VI). She also assessed the data for evidence that anti-drug insulin antibodies were associated with decreased glycemic control (i.e., clinically meaningful neutralizing antibodies). To this end, she relied on an exploratory clinically defined composite endpoint of 1) increase of greater than 10% cross-reactive AIA from baseline AND 2) greater than 0.2% increase in HbA1c AND 3) increase in total insulin dose. At Week 12, 2 patients randomized to MYL-1501D Process V met these criteria compared to no patients randomized to MYL-1501D Process VI. At Week 18, 1 patient randomized to MYL-1501D Process V and 2 patients randomized to MYL-1501D Process VI met the criteria. Dr. Doi concluded (and I concur) that overall the data demonstrate comparable immunogenicity for MYL-1501D produced via Process V and Process VI and provide further support for similar immunogenicity between Lantus and MYL-1501D.

Hypoglycemia

Dr. Doi concluded (and I concur) that the observed hypoglycemic event rates were similar among the patients who received MYL-1501D Process V and the patients who received MYL-1501D Process VI.

Figure 3: Hypoglycemic event rates (episodes/30 days) by visit and treatment (means and SD)



Source: FDA Clinical Review

8. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

9. Pediatrics

The Division determined that this NDA does not trigger the Pediatric Research Equity Act. Therefore, a pediatric assessment is not required.

10. Labeling

Ariane Conrad, Pharm D, and Jason Flint, MBA, of the Division of Medication Error Prevention and Anaylsis (DMEPA) reviewed a pediatric human factors (HF) validation study to assess the ability of pediatric patients to use the Semglee pre-filled pen and a differentiation study to confirm that the intended user population can differentiate the Semglee pre-filled pen from the Humulin R U-500 KwikPen, using the proposed Semglee labeling.

Based on the results of the HF validation study, DMEPA issued recommendations to modify the instructions for use (IFU). DMEPA determined that the changes to the IFU can be implemented without additional validation testing. The differentiation study was undertaken because the proposed Semglee pre-filled pen and the Humulin R U-500 KwikPen (500 units/mL) are similar in appearance (see Figure 4).

Figure 4: Semglee PFP and Humulin R U-500 KwikPen

MYL-1501D PFP	
Humulin R U-500 KwikPen	

Source: FDA DMEPA review

The differentiation study did not exclude the possibility of errors due to confusing the two pens. For that reason, an Information Request (IR) was on July 26, 2019 to the Applicant requesting an assessment of the potential that Semglee and Humulin R U-500 would be prescribed to the same patient. The Applicant provided an assessment that suggested that this would be "highly unlikely." The FDA Clinical Review team agreed that the likelihood of these medications be concomitantly prescribed was low.

CDTL comment: As the team lead of the FDA Clinical Review team, we acknowledge a theoretical risk that a patient could mistakenly use the Semglee pen instead of the Humulin R U-500 KwikPen (or vice versa). However, we believe the actual risk is low, given that it would be unlikely for a patient to have both of these pens in their immediate environment. Moreover, the risk would be expected to be similar for other currently marketed pens that are visually similar to one another (e.g., the various NovoNordisk insulin pens have a similar appearance to one another due to their uniform use of a branded color scheme for NovoNordisk products).

Ariane Conrad also conducted a review of the proposed labels and labeling; she found that the revised labels and labeling for Semglee were acceptable from a medication error perspective and that the Applicant had implemented the recommendations DMEPA had communicated during a previous label and labeling review.

Aman Sarai, BSN, RN, and Ankur Kalola, PharmD, from the Patient Labeling Team in the Office of Prescription Drug Promotion (OPDP) also reviewed the proposed Patient Package Inserts (PPIs) and IFUs for Semglee. They found the PPIs and IFUs acceptable with their recommended changes.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend issuing a **Complete Response**.

I have concluded that the toxicology studies bridging MYL-1501D Process VI and Lantus support an abbreviated non-clinical development program and provide an adequate scientific justification for reliance on FDA's finding of safety for Lantus as reflected in product labeling that describes, among other things, reproduction and early development, carcinogenicity, and chronic toxicology studies. In addition, I concluded that the comparative analytical data, pivotal PK/PD studies (MYL-1501D-1001 and MYL-1501D-1003), the pivotal clinical studies (MYL-GAI-3001 and MYL-GAI-3002) and the additional efficacy, safety, and immunogenicity data from MYL-1501D-3004 provide an adequate scientific bridge between MYL-1501D Process V, MYL-1501D Process VI, and US-Lantus to justify reliance on FDA's finding of safety and effectiveness for Lantus as reflected in the product labeling. These scientific bridges, together with MYL-1501D specific data, establish the safety and effectiveness of MYL-1501D for its proposed conditions of use. I also concluded that the PK/PD study MYL-1501D-1004 provides an adequate scientific bridge between the vial presentation of MYL-1501D and the cartridge/pre-filled pen presentation of MYL-1501D and supports the approval of the vial presentation as well as the cartridge/pre-filled pen presentation of MYL-1501D.

As a result of the identified deficiencies related to the facilities inspection, however, I am unable to conclude that there is a favorable Benefit-Risk assessment for the proposed to-be-marketed (i.e., Process VI) drug product.

See Complete Response Letter for the general description of the deficiencies communicated to the Applicant (Mylan) and the Form FDA 483 sent to the Applicant's development partner (Biocon) for a specific description of the twelve inspectional observations.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICK ARCHDEACON
08/28/2019 02:42:58 PM

LISA B YANOFF
08/28/2019 02:44:54 PM

CLINICAL REVIEW

Application Type	NDA Resubmission
Application Number(s)	210605, eCTD 0045
Priority or Standard	Standard
Submit Date(s)	02/28/2019
Received Date(s)	02/28/2019
PDUFA Goal Date	08/28/2019
Division/Office	DMEP/ODE II/OND
Reviewer Name(s)	Sonia Doi
Review Completion Date	08/26/2019
Established/Proper Name	Insulin glargine
(Proposed) Trade Name	Semglee
Applicant	Mylan
Dosage Form(s)	Subcutaneous injection
Applicant Proposed Dosing Regimen(s)	Individualized
Applicant Proposed Indication(s)/Population(s)	Improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	Recommendation based on review of clinical data: Approval of NDA 210605 for SEMGLEE (insulin glargine) for use as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Recommended Indication(s)/Population(s) (if applicable)	Adults and pediatric patients with type 1 diabetes mellitus and adults with type 2 diabetes mellitus

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Glossary

AC	Advisory Committee
AE	adverse event
AIA	anti-insulin antibody
AR	adverse reaction
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRL	Complete Response Letter
CRO	Contract Research Organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
Nab	neutralizing antibody

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RLD	reference listed drug
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SMBG	self-monitoring blood glucose
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Mylan submitted NDA 210605 for MYL-1501D (proposed trade name Semglee) also referred to as MYL IG, as a 505(b)(2) application: the product intends to rely, in part, on the FDA's findings of safety and effectiveness for Lantus[1], Sanofi's insulin glargine (NDA 021081, approved on 04/20/2000). The original NDA for Semglee was filed over protest. Upon completion of the NDA review, critical deficiencies were identified and a Complete Response Letter (CRL) was issued on 05/18/2018. Among the deficiencies identified, there were two clinical-related major deficiencies: a) due to manufacturing changes made, additional clinical safety and efficacy bridging data, including an assessment of immunogenicity, are needed to establish that the efficacy and safety data generated in the clinical trials using Process V drug product are relevant to the Process VI drug product intended for marketing; and b) bridging data between the cartridge and vial presentations necessary for approval of the vial presentation, due to the addition of polysorbate 20 to the composition of the vial presentation. To address these deficiencies, the Applicant completed a study to establish a clinical bridge between Process V and Process VI products and a study to establish a pharmacokinetic/pharmacodynamic (PK/PD) bridge between the vial and the prefilled cartridge presentations. A response to FDA's CR letter and the updated NDA application, including the data from these studies, were submitted for review on 02/28/2019.

Insulin glargine is a long-acting analog of human insulin and its primary sequence differs from human insulin by three amino acids: glycine instead of asparagine at position A21, and two arginines added to the C-terminus of the B-chain. These amino acid changes result in slow and stable release of insulin into the circulation. The amino acid sequence of MYL-1501D is identical to that of Lantus, and while they are both produced by rDNA technology, MYL-1501D is produced using the yeast *Pichia pastoris* and Lantus is produced using the bacteria *E.coli*. The MYL-1501D product is proposed to be marketed in two presentations: a 10-mL vial and a 3-mL cartridge/prefilled pen. MYL-1501D is intended for subcutaneous injection to be administered once daily with an indication identical to that of Lantus, i.e., to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In the original NDA submission, the Applicant submitted comparative analytical testing, PK/PD

[1] In this review Lantus refers to the U.S.-approved Lantus, unless otherwise identified.

data and comparative clinical data to justify reliance, in part, on FDA's findings of safety and effectiveness for Lantus to approve MYL-1501D. While the review of the Phase 3 clinical trials conducted with Process V MYL-1501D supported the conclusion that Process V MYL-1501D was non-inferior to Lantus in patients with T1DM and T2DM, a clinical bridging study to demonstrate sufficient similarity between Process V and Process VI was required to support reliance of the product intended for marketing (Process VI) on the reference listed drug (RLD) Lantus. The results of Study MYL-1501D-3004 have demonstrated similarity with regard to efficacy and safety, including immunogenicity between the product to-be-marketed (Process VI) and the product utilized in clinical trials (Process V), providing support for reliance of MYL-1501D manufactured by Process VI on the RLD, Lantus.

The clinical data reviewed by Dr. Rauschecker in the original NDA together with the new clinical data of the current NDA resubmission support the safety and effectiveness of MYL-1501D (Semglee) from the perspective of the clinical review. However, the Office of Pharmaceutical Quality (OPQ) inspection (conducted on 24 June - 5 July 2019) of the drug substance and drug product manufacturing facility in Malaysia (BIOCON) to evaluate correction of 40 deficiencies cited in the CRL to the original NDA submission, resulted in 12 observations.

Recommendation: The data from MYL-1501D-3004 provide sufficient additional clinical safety and efficacy bridging data, including its assessment of immunogenicity, to establish that the efficacy and safety data generated with the Process V drug product is relevant to the Process VI drug product (i.e., the to-be-marketed product) and can be used to support a determination that the proposed to-be-marketed product is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus. Based on review of the overall clinical data submitted under NDA 210605, the Clinical Reviewer recommends approval of SEMGLEE (insulin glargine) for use as an adjunct to diet and exercise to improve glycemic control in adults and children with T1DM and adults with T2DM. However, failure to provide timely adequate responses/action to resolve all 12 OPQ observations will impact the approvability of this NDA.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Mylan has resubmitted a 505(b)(2) application (NDA 210605) for MYL-1501D (Semglee) relying, in part, on FDA's findings of safety and effectiveness for Lantus[1]. The objective of the resubmission is to address the deficiencies listed in the CRL issued in response to the original NDA submission. One of the major clinical deficiencies noted in the original application was due to a change in the drug substance manufacturing processes. The drug product utilized in clinical trials to support the NDA was manufactured using Process V, while the proposed to-be-marketed product follows "Process VI". The decision to change manufacturing processes was due to a recommendation of the European Medicines Agency (EMA) to reduce [redacted] (b) (4) of the drug substance. The reduction [redacted] (b) (4) in Process VI product resulted in changes in impurity profiles compared to the Process V product. The Applicant conducted comparability studies, along with comparative toxicity studies, and PK/PD studies between Process V and Process VI but did not submit clinical studies to assess potential differences in immunogenicity between the two products. To address this deficiency, the Applicant submitted the results from an additional clinical study (MYL-1501D-3004) in patients with type 1 diabetes mellitus (T1DM) for 18 weeks, comparing the efficacy and safety, including immunogenicity of the products manufactured by Process V and Process VI. The primary efficacy endpoint of Trial 3004 was change in HbA1c from baseline at Week 18, with a pre-defined non-inferiority margin of 0.4%. The result of the primary endpoint analysis showed a mean difference between Process VI and Process V in HbA1c change from baseline of -0.04% (95% CI -0.18, 0.1), meeting the primary objective of Trial 3004. There were no clinically significant differences between the safety profile and immunogenicity of Process V and Process VI in Study MYL-1501D-3004. The majority of the patients had positive anti-insulin antibody (AIA) assays at baseline. The number of AIA+ patients was similar across the Process V and Process VI treatment groups, both at baseline and at Week 18. The number of patients with positive assays for neutralizing antibody (nAb) against insulin was very small in both treatment groups, with no statistical difference noted between groups.

In conclusion, the clinical data support the safety and effectiveness of Semglee (Process VI, intended for marketing). The overall risk-benefit assessment appears favorable for the use of Semglee to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diabetes mellitus is a serious chronic medical condition characterized by hyperglycemia and includes two main types: T1DM and T2DM. • T1DM is caused by autoimmune destruction of the pancreatic beta cells, which leads to impaired insulin production and secretion, and impaired glucose metabolism. • T2DM is characterized by hyperglycemia either due to insulin resistance or a deficiency of insulin, and is often associated with other metabolic derangements, such as dyslipidemia, hypertension, and obesity. • Diabetes mellitus affects over thirty million people in the United States, the majority (90-95%) of these patients have T2DM, according to the Centers for Disease Control (CDC)[1]. • Acute life-threatening complications of T1DM include diabetic ketoacidosis due to insulin deficiency, while chronic complications of both T1DM and T2DM include cardiovascular disease, retinopathy, nephropathy, and neuropathy.	Both T1DM and T2DM are serious, life-threatening conditions that can lead to serious morbidity and mortality if left untreated.
Current Treatment Options	• The results of the Diabetes Control and Complications Trial (DCCT)[2-4] demonstrated that intensive insulin therapy resulted in improved glycemic control as measured by HbA1c, which was associated with improved clinical outcomes in patients with T1DM. • Due to the depletion of pancreatic beta cells which produce insulin, patients with T1DM require exogenous insulin for survival. Pramlintide, an amylin-mimetic, is also approved as adjunctive therapy to insulin. • Treatment options for T2DM include lifestyle modifications, usually	Intensive insulin therapy is the standard of care for patients with T1DM. Patients with T2DM often require multiple agents for glycemic control, and due to the progressive nature of the disease may also require insulin to achieve glycemic targets.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	followed by the addition of one or multiple different medications[5]. There are currently multiple classes of pharmacologic treatments for T2DM, with multiple members of each class, including biguanides, sulfonylureas, insulin and insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose cotransporter (SGLT)-2 inhibitors.	
Benefit	• The Applicant is relying, in part, on FDA's finding of safety and effectiveness for the listed drug Lantus. Comparative clinical data from Trial 3001 (T1DM subjects) and Trial 3002 (T2DM subjects) demonstrated that MYL-1501D in combination with other antihyperglycemic agents (prandial insulin in Trial 3001 and oral antihyperglycemic agents in Trial 3002) was non-inferior to Lantus in change in HbA1c from baseline to Week 24. As the Phase 3 clinical trials for MYL-1501D were manufactured by Process V and the product intended for marketing is manufactured by Process VI, a comparative study (Trial 3004) was conducted in T1DM patients to establish a clinical bridge between Process V and Process VI. Results of Trial 3004 demonstrated similarity of safety and effectiveness between Process V and Process VI, which supports a conclusion of similarity of benefit between Process V and Process VI drug products.	Results of the Phase 3 clinical trials (Trial 3001 and Trial 3002) conducted in patients with T1DM and T2DM support the reliance of MYL-1501D manufactured by Process V on the FDA's findings of safety and effectiveness for the reference listed drug (RLD) Lantus. The comparative trial (Trial 3004) established a clinical bridge between MYL-1501D manufactured by Process V and MYL-1501D manufactured by Process VI, thus supporting reliance of the product intended for marketing (MYL-1501D Process VI) in part, on FDA's findings of safety and effectiveness for the RLD Lantus.
Risk and Risk Management	• The risks identified for MYL-1501D Process V in the Phase 3 pivotal trials were similar to the previously identified risks associated with Lantus use. No new safety signals were identified for the MYL-1501D Process V. Similarity of the safety profile between the products manufactured by Process V and Process VI was	Collectively, results of the pivotal Phase 3 trials and the comparative clinical trial support the conclusion that the risks associated with the MYL-1501D product intended for marketing (Process VI) are no different from those

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	demonstrated by the results of the comparative clinical Trial 3004.	associated with the use of the RLD Lantus.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

Please refer to information provided in the original NDA review by Dr. Mitra Rauschecker, submitted to DARRTS on 4/30/2018. There has been no updated information for this Section since the submission of the original review.

2.2. Analysis of Current Treatment Options

There are currently 12 pharmacological classes of medications approved in the US to treat diabetes. Many of these products are also approved as fixed combination drug products. Since the clinical review of the original NDA submission, dated 4/30/2018, there were a few additional medications approved. An updated list of therapeutic options for the management of diabetes mellitus available to date is presented in Table 1.

Table 1: Approved therapeutic options for the management of diabetes mellitus*

Pharmacologic Class	Antihyperglycemic Drug Products
ALPHA-GLUCOSIDASE INHIBITORS	Acarbose; Miglitol
AMYLIN MIMETICS	Pramlintide
BIGUANIDES	Metformin
BILE ACID SEQUESTRANTS	Colesevelam
DOPAMINE-2 AGONISTS	Bromocriptine
DPP-4 INHIBITORS	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 RECEPTOR AGONISTS	Albiglutide; Dulaglutide; Exenatide; Exenatide extended-release; Liraglutide; Lixisenatide; Semaglutide
INSULINS AND INSULIN ANALOGUES	Inhaled insulin (human); Insulin aspart; Insulin glulisine; Insulin lispro; Insulin isophane (NPH); Insulin regular (human); Insulin glargine; Insulin detemir; Insulin degludec; Pre-mixed insulins (various)
MEGLITINIDES	Nateglinide; Repaglinide
SGLT-2 INHIBITORS	Canagliflozin; Dapafliflozin; Empagliflozin, Ertugliflozin
SULFONYLUREAS	Chlorpropamide; Glimepiride; Glipizide; Glipizide extended-release; Glyburide; Tolazamide; Tolbutamide
THIAZOLIDINEDIONES	Pioglitazone; Rosiglitazone

*Note that only insulins, insulin analogues, and amylin mimetics are approved for T1DM.
Source: Center Watch, June 2019 FDA approved drugs (https://www.centerwatch.com/drug-information/fda-approved-drugs/medical-conditions/D)
DPP-4, dipeptidyl peptidade-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Please refer to information provided in the original NDA review by Dr. Mitra Rauschecker, submitted to DARRTS on 4/30/2018. There has been no updated information for this Section since the original review was completed.

3.2. Summary of Presubmission/Submission Regulatory Activity

NDA 210605 was submitted on 04/27/2017 as a 505(b)(2) pathway for insulin glargine injection 100 Units/mL, relying in part on FDA'S findings on safety and effectiveness for LANTUS. This

application consisted of two Phase 1 PK/PD studies and two Phase 3 clinical trials. The Phase 3 trials were conducted to evaluate the formation of insulin antibodies and potential impact of antibodies on safety and efficacy. Due to change in the manufacturing facility, the product to be-marketed (Process VI) was manufactured in a different facility than the product used in the Phase 3 trials (Process V). The Applicant submitted Study MYL-1501D-1001, which was a single-dose 3-way crossover euglycemic clamp to demonstrate PK/PD similarity between the Process V and Process VI products. The Agency informed the Applicant that a single-dose euglycemic clamp study is not adequate to evaluate potential differences in immunogenicity between the two products nor to assess potential differences in clinical and safety outcomes due to differences in impurities between the two products.

In addition, it was noted that the trials had been conducted with the cartridge/prefilled pen presentation and the Applicant intended to include the vial presentation in the product label. However, the formulations of the two presentations were different: the vial excipient contained polysorbate 20 that is not present in the cartridge formulation.

In the Refuse-to-File determination, the Agency informed the Applicant of two critical deficiencies identified in the NDA: lack of adequate bridging data from Process V to Process VI and lack of a PK/PD bridge between the cartridge and vial presentations. On August 31, 2017, the Applicant requested the NDA to be Filed over Protest. Upon completion of the NDA review, a Complete Response (CR) Letter was issued on 05/18/2018 due to critical deficiencies identified. An amendment submitted on 05/11/2018, pertaining to antimicrobial effectiveness testing, was not reviewed due to the short time between submission and review date, and was to be incorporated in the response to the CR Letter.

A response to FDA's CR Letter and updated NDA package were submitted for review on 02/28/2019 and contained responses to all deficiencies listed in the CR Letter. Each summarized deficiency (primary bullet) and respective summarized Mylan's response (secondary bullet) are listed below:

- While approval was requested for Mylan's insulin glargine (MYL-1501D) manufactured using Process VI in Malaysia, the MYL-1501D product used in trials supporting the NDA was manufactured using Process V in India. To resolve this deficiency, the Applicant was required to submit additional clinical safety and efficacy bridging data, including assessment of immunogenicity between Process V and Process VI products.
    - To address this deficiency, the Applicant conducted Study MYL-1501D-3004 in patients with T1DM to establish safety and efficacy similarity between Process V and Process VI. Results of this study were submitted for review.
- Since the PK/PD studies were conducted only with the cartridge pen presentation, the Applicant was requested to submit a PK/PD study bridging the vial and the cartridge presentations.

    - The Applicant submitted results of Study MYL-1501D-1004 to demonstrate a PK/PD bridge between vial and cartridge (prefilled pen) presentations.
- During a facility inspection of Biocon (Malaysia), a manufacturing facility for this NDA, objectionable conditions were noted. Satisfactory resolution of the observation is required before this NDA can be approved.
    - The 40 Corrective and Preventive Actions (CAPAs) items noted in the Biocon facility inspection were addressed and CAPA execution updates were submitted in the NDA resubmission package for review.
- CMC microbiology deficiencies included lack of method suitability data for endotoxin, sterility, and antimicrobial effectiveness testing (AET), and lack of AET data supporting the product expiry from stability.
    - The Applicant conducted and submitted AET and bacterial endotoxin (BET) method validation for review.
- The Applicant was recommended to revise the methods used for the determination of high molecular weight proteins and product related substances, to include equations used for impurity calculations in the high-performance liquid chromatography (HPLC) and size exclusion chromatography (SEC) impurity methods, and HPLC peak resolution criteria of not less than 2.0 for impurities to the system suitability.
    - Equations for the HPLC and SEC method were included in Section 3.2.S.4.2 and Section 3.2.P.5.2; and the HPLC peak resolution criteria of not less than 2.0 for impurities to the system suitability of the RP-HPLC method were provided.
- The Applicant was requested to provide additional information for aged drug product.
    - Mylan performed analysis comparing individual impurity profile for aged products and accelerated stability studies and provided results for review.
- Mylan was requested to address human-factor (HF) related deficiencies, which included insufficient number of untrained injection naïve pediatric patients in each user group of the HF validation study.
    - Mylan submitted for review an additional HF pediatric validation study and a study for the intended user population for product differentiation.
- FDA requested changes to several areas of the Prescribing Information (PI), and also to carton and container labeling.
    - Mylan made the changes requested and resubmitted updated versions of the PI, carton and container labeling for review.
- FDA requested to resubmit the proposed proprietary product name with the response to the CR Letter.
    - Proprietary name and associated commercial information have been submitted.
- FDA requested the Applicant to describe in detail any significant changes or findings in the safety profile, and specifically to address: discontinuation due to adverse events (AEs), serious adverse events (SAEs), and common AEs, as well as to incorporate new safety data presented in the same format as the original submission, tabulations of the new safety data combined with the original application data, including tables that compare frequencies of

AEs in the original application with the retabulated frequencies, and provide separate tables for the frequencies of AEs occurring in clinical trials. It was also requested that Mylan presented a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials, describing any new trends or patterns identified.
    - Mylan informed that no safety findings to market experience have been identified during the reporting period – a safety response document was submitted.
- Mylan was requested to provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. Also, to provide narrative summaries for SAEs.
    - Mylan informed that no deaths or SAEs occurred in the new trials. CRFs and narrative summaries for Study MYL-1501D-3004 were provided in the Safety Response document and Appendix 16.1.3
- FDA requested the Applicant to describe any information that suggests a substantial change in the incidence of common, but less serious AEs between new data and original application; provide updated information for the clinical studies/trials; provide a summary of worldwide experience on the safety of this product, including an updated estimate of use for product marketed in other countries.
    - Information was provided in the Safety Response document, in the NDA re-submission.
- Provide English translations of current approved foreign labelling not previously submitted.
    - English translations were provided in the Safety Response and labeling documents in the NDA re-submission.

3.3. Foreign Regulatory Actions and Marketing History

In response to the FDA's request (CR Letter) to provide a summary of worldwide experience on the safety of the MYL-1501D product and updated estimate of use for product marketed in other countries, Mylan provided the following information:

- Insulin glargine manufactured by Process V has been approved in Uganda (since 2016) and in Guatemala (since June 2017) under the tradename ENDULIN. In 2018, Mylan's insulin glargine manufactured by Process VI (SEMGLEE) was approved in Australia and European Union (EU).
- The cumulative patient exposure provided for the period of June 2017 to December 2018 was 12,748 patient-time exposure in years (PTY) for Process V and 2,269 PTY for Process VI. The Applicant calculated PTY based on the formula: PTY= Total mg sold/WHO DDD X 365, where the WHO DDD is the World Health Organization defined daily dose for insulins = 40.
- No safety findings from the foreign marketing experience have been identified during the period of June 2017 to December 2018.

An updated marketing information was provided by the Applicant in response (dated May 28,

2019) to an Information Request sent by DMEPA and indicates that Semglee (Process VI) is currently approved in Australia, European Union (EU) and New Zealand. However, Semglee is currently marketed in the EU region only, which includes Bosnia, Croatia, Denmark, Poland, Slovakia and United Kingdom.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspection for the original NDA consisted of three domestic sites and one foreign clinical site as well as the sponsor, and the inspection findings revealed no regulatory violations. No further action was required regarding site inspection.

4.2. Product Quality

MYL-1501D, also referred to as MYL IG is insulin glargine produced by recombinant DNA technology using *Pichia pastoris*. The product intended for marketing is manufactured at the BIOCON facility in Malaysia. In the review of the original NDA submission, the Office of Pharmaceutical Quality (OPQ) conducted inspection of Biocon (Malaysia) and identified 40 objectionable conditions at the facility requiring corrective actions and recommended issuing a CR Letter. The facility was issued a Pre-Approval Inspection (PAI) while waiting for re-evaluation.

In the resubmission, the Applicant stated that all 40 Corrective and Preventive Action (CAPA) items corresponding to the comments of the FDA field investigator have been closed as of September 19th, 2018. Details for the commitments, actions implemented and status for each of the 40 CAPAs were provided by the Applicant in Annexure 1 and Annexure 2, included in the NDA re-submission package.

OPQ review of the resubmitted application included inspection of the Biocon manufacturing facility in Malaysia that was conducted during the period of 06/24/19 to 07/05/2019. The inspection was focused on the effectiveness of the corrective actions, that included primarily: (b) (4) (b) (4). In addition, this inspection reviewed data and record integrity, laboratory controls, and device production according to 21CFR820. The OPQ findings on the inspection conducted for the period 06/24/19 to 07/05/2019 resulted in 12 objectional conditions (listed in Form FDA-483) that included repeat observations demonstrating failure in implementing effective corrective actions and indicated lack of an effective quality

management system. Based on the inspection findings, OPQ recommended withhold approval for drug and pen device. A response to the FDA's findings is expected by July 26th (PDUFA date is August 28th).

For complete information, please refer to the OPQ review by Dr. Muthukumar Ramaswamy.

4.3. Clinical Microbiology

The 12 objectional conditions identified by OPQ at the BIOCON Malaysia manufacturing facility (b) (4)

(see Section 4.2 above). A response to clinical microbiology deficiencies will be evaluated as part of the responses to all the findings to resolve the OPQ withhold recommendation.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to information in the Nonclinical Review section by Dr. Arulasanam Thilagar of the original NDA submission.

4.5. Clinical Pharmacology

This section contains a summary of the clinical pharmacology review findings. For complete information please refer to the Clinical Pharmacology Review by Dr. Jing Niu.

The Applicant submitted Study MYL-1501D-1004 and Study MYL-1501D-1003 to demonstrate pharmacokinetic/pharmacodynamic (PK/PD) similarities between the vial and pen presentations as outlined by Dr. Jing Niu in the original NDA review. Study 1501D-1004 was conducted to demonstrate PK/PD similarity between vial and cartridge presentations. This study was necessary because the vial formulation contains polysorbate 20 as an excipient, which is not included in the cartridge formulation. Study 1501D-1003 was conducted to demonstrate PK/PD similarity between the product intended for marketing (Process VI) and the reference listed drug, Lantus, as well as between Process VI and the product used in pivotal clinical trials (Process V). A summary of the clinical pharmacology review findings is outlined below:

1. Study MYL-1501D-1004

The Clinical Pharmacology reviewer noted that in study MYL-1501D-1004, roughly 20% of PK profiles were excluded from the PK analysis due to meeting the pre-defined exclusion criteria "less than 50% of concentration (7 measurements) above LLOQ post dosing". PD data was available for all 45 subjects for analysis. While the total number of PK profiles excluded (18 out of 40) was unusually high considering the other PK/PD studies submitted by the Applicant, the statistical analysis performed by Dr. Jing Niu met the pre-specified statistical criteria for PK and

PD comparability (GMR and 90% CI within 80-125%). Dr. Niu also conducted a sensitivity analysis excluding corresponding PD observations for the primary PD endpoint and the results did not deviate from the pre-specified criteria for PD comparability.

The issue of acceptability of the unusually high PK profile exclusion in Study MYL-1401D-1004 was discussed internally with Senior Leadership Team within the Office of Clinical Pharmacology (OCP). The OCP team reached general consensus on accepting the study results towards demonstration of PK/PD comparability supported by the balanced number of exclusion between treatments and by the corresponding PD data comparability analysis. The Clinical Pharmacology reviewer concluded that the Study MYL-1501D-1004 PK/PD data was comparable between the vial (containing polysorbate) and the cartridge (without polysorbate) formulations.

2. Study MYL-1501D-1003

From a total of 95 subjects randomized, 88 subjects completed at least 2 periods of the study without major protocol deviation and were included in the PK analysis set. Specific periods were excluded from PK or PD analysis once the periods could not meet the protocol pre-defined requirements. Dr. Niu's review findings for Study MYL-1501D-1003 indicated that the PK and PD profiles appear similar among Process V, Process VI and US-Lantus.

Based on the review of the pharmacology data submitted under the NDA 210605 resubmission, the OCP/Division of Clinical Pharmacology 2 concluded that the results of both, Study MYL-1501D-1003 and Study MYL-1501D-1004 are acceptable.

4.6. Devices and Companion Diagnostic Issues

Review of the original NDA submission: There were no issues raised by the Center for Devices and Radiological Health (CDRH) reviewer (Dr. Rong Guo) on the response to the consult requested to evaluate the safety and functionality of the proposed prefilled pen injector submitted in the original NDA submission. CDRH recommended approval of the device constituent of the combination product in the original NDA review.

Review of the NDA re-submission (Study MYL-1501D-3004): The focus of the review on devices and companion diagnostic issues in Study MYL-1501D-3004 is to identify whether the issues reported with devices or companion diagnostic had a significant impact on differences in effectiveness and safety between Process V and Process VI products.

In Study MYL-1501D-3004, the study medication (insulin glargine MYL-1501D) administered to each treatment group, i.e., Process V and Process VI, used identical prefilled pen/needle and glucometer devices. The total number of patients reporting device (basal and mealtime insulin pens, glucometer, and needle) complaints was 19 in the Process V group and 15 in the Process VI group. However, only a single device complaint (needle) was reported as leading to an AE (Grade 1 injection site hemorrhage) in the Process VI group (see Table 2).

Table 2: Summary of device complaints (Safety population)

Device type	Process V N=108 n (%)	Process VI N=110 n (%)
At least 1 device complaint[a]	19 (17.6)	15 (13.6)
Basal insulin pen	8 (7.4)	8 (7.3)
Device complaints leading to dosing error or no dose delivered	0	4 (3.6)
Device complaints leading to an AE	0	0
Other complaints	8 (7.4)	4 (3.6)
Glucometer	5 (4.6)	3 (2.7)
Device complaints leading to dosing error or no dose delivered	1 (0.9)	0
Device complaints leading to an AE	0	0
Other complaints	4 (3.7)	3 (2.7)
Meal time insulin pen	10 (9.3)	3 (2.7)
Device complaints leading to dosing error or no dose delivered	5 (4.6)	1 (0.9)
Device complaints leading to an AE	0	0
Other complaints	6 (5.6)	2 (1.8)
Needle	2 (1.9)	1 (0.9)
Device complaints leading to dosing error or no dose delivered	2 (1.9)	1 (0.9)
Device complaints leading to an AE	0	1 (0.9)
Other complaints	0	0

a Patients could have more than 1 device complaint
Source: Excerpted from Table 22, Clinical Study Report (CSR) file.

No clinically significant safety issues were identified with the use of the devices for insulin administration or glucometer in Study MYL-1501D-3004. See further details on device-related treatment emergent adverse events (TEAEs) under Section 8.4.4.

4.7. Consumer Study Reviews

Dr. Ariane Conrad, Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors (HF) validation study reports, the differentiation study to assess differentiation between Mylan's pen and Lilly's Humulin R U-500 KwikPen (due to similar appearances between the two pens), and the proposed labeling submitted by the Applicant in the original NDA submission.

In the NDA resubmission, Mylan provided the results of a non-dosing differentiation study conducted with 126 participants for selection between the Semglee pen and the Humulin U-500 KwikPen. A total of 4 participants selected the Humulin U-500 KwikPen rather than the Semglee pen, two of which were untrained participants who chose the pen that was most familiar to them (Humulin U-500 KwikPen).

To assess the incidence of identification errors, DMEPA sent an Information Request (dated 05/28/2019) for Mylan to provide an analysis of postmarketing serious and nonserious

medication error cases, adverse event cases, and complaints associated with product selection errors between Semglee and other insulin products including Humulin R U-500. Mylan informed that a search of their global safety database for post-marketing cases for insulin glargine medication errors contained 18 cases. However, no cases were specifically reported for Semglee nor confirmed Mylan as the Manufacturing Authorization Holder. Mylan search of the safety database reviewed cases from all territories, including 6 countries in the EU region (Bosnia, Croatia, Denmark, Poland, Slovakia and UK) where Semglee is currently marketed, Australia and New Zealand where Semglee is approved but not currently marketed, and countries where Mylan markets insulin glargine in vial presentation and not in pen presentation (For complete information please refer to Mylan's response to DMEPA IR, dated 06/04/2019). It is of note that a negative finding in the EU is not a meaningful result to assess differentiation errors between Semglee and Humulin U-500 because Humulin U-500 is not a product marketed in EU at this time.

Figure 1: Insulin pen Humulin U-500 (top) and insulin pen Semglee (bottom)

Internal meetings were held between the DMEP and DMEPA review teams to discuss: a) the impact of similar color between Semglee and Humulin U-500 pens (Figure 1) on identifying the correct pen for use, and b) to discuss possible mitigation approaches.

Since Humulin U-500 is indicated as both basal and prandial insulin use, the possibility exists that a patient be using concomitantly Semglee as basal insulin and Humulin U-500 as prandial insulin, in which case there could be a risk for error in identifying the correct insulin pen to use. Another possible scenario would be a patient who switches from Humulin U-500 to Semglee and has not discarded the Humulin U-500 pen. While the risk for adverse events, e.g., hypoglycemia exists in principle, the expert opinion of clinicians in DMEP is that the risk of serious adverse event from differentiation error between Semglee and Humulin U-500 pen appears to be small. This opinion is based on the following: a) Humulin U-500 is currently used by a small number of patients because Humulin U-500 is concentrated formulation of insulin indicated to patients who require more than 200 units of insulin/day; b) Dialing features of the Semglee pen (dials in 1-unit increment) is different from the dialing features of the Humulin U-500 pen (dials in 5-unit increments).

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

A single clinical study (MYL-1501D-3004) has been submitted for review in the resubmission NDA package. The complete MYL-1501D Development Program includes 7 pivotal studies (4 PK/PD trial and 3 safety/efficacy clinical trials) that are listed in Table 3. In the original NDA application, two Phase 3 clinical trials (MYL-GAI-3001 and MYL-GAI-3002) were reviewed by Dr. Mitra Rauschecker (Please refer to Clinical Review of the original NDA for complete information on these two trials). The Applicant has also conducted 4 supportive studies: FFP-112-01 (PK/PD), CLG031/BIO012/DM/GLA/2007 (safety/efficacy), FFP-112-02 (safety/efficacy), and MYL-1501D-3003 (safety/efficacy) that will not be the focus of this review.

Table 3: Tabular listing of all pivotal clinical studies of the MYL-1501D Developmental Program

Study ID/Type of Study	Primary Objectives	Study Design	Number of Subjects	Duration of Treatment
GLARGCT100111 PK/PD	To compare the relative PK/PD properties of MYL1501D, Lantus-US and Lantus-EU	Randomized, double-blind, single-dose, 3-way crossover euglycemic clamp; active control	T1DM patients 114 randomized, 112 completed	3 single doses (MYL1501D), 1 dose (Lantus US) and 1 dose (Lantus EU) Washout: 5-28 days between doses
MYL-1501D-1001 PK/PD	To demonstrate biosimilarity with regard to the total exposure, based on the M1 metabolite of MYL1501D and Lantus US	Randomized, double-blind, single dose, 3-way crossover, euglycemic glucose clamp; active control	T1DM patients 116 randomized, 113 completed	3 single doses (MYL1501D Process V, MYL1501D Process VI, and Lantus US) Washout: 5-28 days between doses.
MYL-GAI-3001 Safety/Efficacy	To test for non-inferiority in change in HbA1c from baseline to Week 24 between MYL-1501D and Lantus US	Open-label, randomized, parallel assignment; active control. Used prefilled pen presentation	T1DM patients 558 randomized, 517 completed	Run-in period: 6 weeks; Randomized comparative treatment: 52 weeks
MYL-GAI-3002 Safety/Efficacy	To test for non-inferiority in change in HbA1c from baseline to Week 24 between MYL-1501D and Lantus US	Open-label, randomized, parallel assignment; active control Lantus	T2DM patients 560 randomized, 490 completed	Randomized comparative treatment period with titration: 12 weeks. Randomized comparative treatment period with minimal titration: 12 weeks. Total treatment period: 24

Study ID/Type of Study	Primary Objectives	Study Design	Number of Subjects	Duration of Treatment
				weeks
MYL-1501D-3004 Safety/Efficacy	To compare safety and efficacy of MYL-1501D product Process VI and Process V at week 18, when administered in combination with mealtime insulin lispro	Randomized, double-blind, parallel assignment	T1DM patients 219 randomized, 205 completed	Screening Period: 2 weeks Run-in period: 4 weeks Treatment period: 18 weeks Safety Follow-up: 2 weeks Total treatment period: 26 weeks
MYL-1501D-1003 PK/PD	To demonstrate PK and PD equivalence of insulin glargine between MYL-1501D (Process V), MYL-1501D (Process VI) and US Lantus with respect to glucose infusion rate and insulin glargine metabolite 1 concentration	Randomized, double-blind Using cartridges	Healthy subjects 95 randomized, 74 completed	Screening visit: 28 days before treatment period Treatment Period: 6 dosing visits 5-14 days apart Follow-up Visit: 1-7 days after last dosing visit
MYL-1501D-1004 PK/PD	To demonstrate PK and PD equivalence of MYL-1501D Process VI formulation in cartridge vs. vial	Randomized, single-dose, fully replicated, 4-way crossover	Healthy subjects 48 randomized, 45 completed	5 weeks per subject Treatment period: 4 single-dose administrations, 2 of each test product, separated by 5-21 days between visits.

Source: Table adapted from Table 1, Tabular Listing file submitted in the NDA package.

5.2. Review Strategy

This clinical review focuses on the efficacy and safety findings of Study MYL-1501D-3004.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study MYL-1501D-3004

6.1.1. Study Design

Overview and Objective
Study MYL-1501D-3004 was conducted to complete an adequate scientific bridge from the drug product used in the clinical trials and the drug product intended for commercial use. The MYL-1501D product submitted for approval was manufactured in a facility in Malaysia using Process VI, while the product used to conduct the Phase 3 clinical trials was manufactured in a facility in India using Process V. The objective of Study MYL-1501D-3004 is to provide data on efficacy and clinical safety, including assessment of immunogenicity of the Process V and Process VI products. This study was conducted at 88 study sites in the US.

Trial Design
MYL-1501D-3004 is a multicenter, double-blind, randomized, parallel-group Phase 3 trial conducted in patients with T1DM treated with MYL-1501D Process V or MYL-1501D Process VI. Insulin MYL-1501D was administered in combination with mealtime insulin lispro. A total of 219 patients were randomized.

This study was comprised by a 4-week run-in period, followed by an 18-week randomized treatment period and a 2-week safety follow-up period, for a total duration of 26 weeks. A diagram of the study design is outlined in Figure 2.

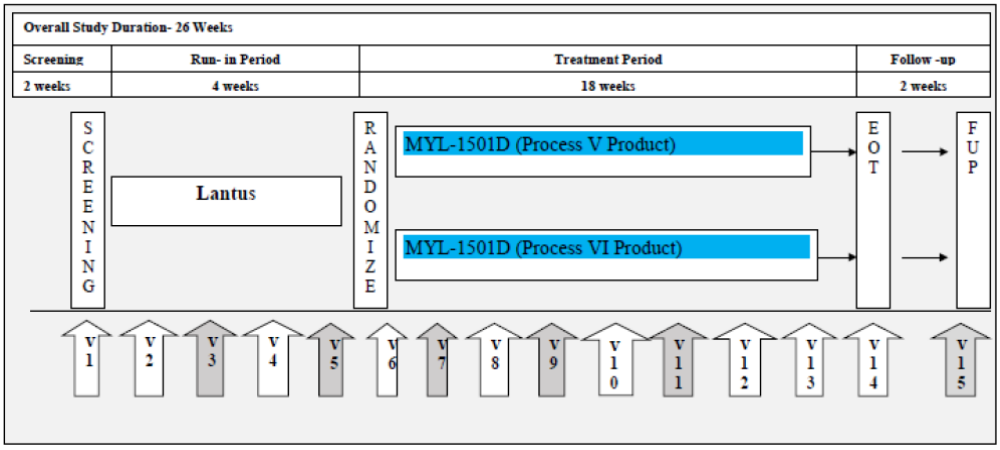

Figure 2: Diagram of study design
Source: Excerpted from Figure 1, CSR

During the run-in period, all patients received Lantus (insulin glargine) as basal insulin and Humalog (insulin lispro) as prandial insulin. The doses of Lantus and Humalog were titrated as needed to maintain glucose control during the run-in period. At the end of the run-in period patients were randomized at 1:1 ratio to receive either MYL-1501D produced by Process V or MYL-1501D produced by Process VI, stratified by time of administration (morning and evening). During the treatment period, patients self-administered the investigational product (IP) using the prefilled pen once daily, in combination with mealtime Humalog for 18 weeks.

Insulin dose titration of Lantus during the run-in period and the IP during the treatment period were guided by self-monitoring of blood glucose (SMBG) glucose assessments and by a titration committee. SMBG measurements, insulin dose adjustments, and reason for insulin dose changes were reviewed by the committee on a daily basis.

The schedule of visits included assessments and documentation that patients received training on self-management of diabetes, lifestyle modification measures, and monitoring to prevent complications.

Study Endpoints
The primary efficacy endpoint was change in HbA1c from baseline up to Week 18.

Secondary efficacy endpoints were:
- Change in fasting plasma glucose (FPG) from baseline
- Change in basal, mealtime and total insulin dose per body weight (Unit/kg) from baseline
- Change in 8-point self-monitored blood glycose (SMBG) profile from baseline

Safety endpoints were:
- Immunogenicity: incidence and change from baseline in the relative levels of anti-drug antibody (ADA).
- Hypoglycemic events: incidence and 30-day rate
- Occurrence of AEs, including local and systemic reactions
- Device-related safety assessment.

Statistical Analysis Plan
The primary efficacy endpoint analysis was performed to establish non-inferiority of the HbA1c mean change from baseline to Week 18 obtained with the Process VI product *versus* that obtained with the Process V product. A total of 172 patients was calculated to demonstrate a non-inferiority margin of 0.4% using a 2-sided 95% confidence interval and a 90% power. A total of 202 patients were planned to account for a maximum of 15% of subjects not eligible for the PP analysis. The true treatment difference and standard deviation (SD) was based on the previous Study MYL-GAI-3001.

Analyses were performed as described in the Statistical Analysis Plan (SAP), version 2.0, dated 10/18/2018 and used a mixed model for repeated measures (MMRM) approach. Missing data were imputed using the missing-at-random (MAR) assumption. Data from patients who received rescue medication and patients who switched to their own medication were treated as missing values. The Applicant performed two types of sensitivity analyses to test for robustness of the primary endpoint analysis: sensitivity to analysis set (using the PP population) and sensitivity to missing data assumptions.

For secondary efficacy endpoints, the Applicant used descriptive statistics presented by treatment group for actual variables and change from baseline to scheduled visits. Comparisons between treatment groups were performed using the MMRM approach without imputing missing values.

Protocol Amendments
The original protocol was dated 09/08/2017 and a protocol amendment (Version 2.0) was submitted on 02/02/2018. The key protocol changes are summarized below:

- Titration committee added to guide the dosing of MYL-1501D during treatment period and Lantus during run-in period
- Added option of being on stable dose for Levemir or Toujeo for at least 3 months at screening (previously only Lantus was allowed as treatment option)
- Updated the requirement for being in supine position from 10 mins to 5 mins prior to an ECG
- Review of results of the 8-point SMBG measurements removed from Visit 7 (Week 1), Visit 8 (Week 2), Visit 9 (Week 4) and Visit 11 (Week 9)
- Removed fasting plasma glucose assessment at Visit 13 (Week 15)
- Primary analysis to include all available outcome data from all randomized patients regardless of treatment discontinuation and use multiple imputation approach for missing data that more appropriately takes treatment adherence into account
- Primary efficacy population to include all randomized subjects – irrespective of subjects having post-baseline measurement

Clinical Reviewer's Comment: This amended protocol was reviewed by the Statistical Reviewer (Dr. Anna Ketterman) who made two recommendations: a) to use a tipping point approach in sensitivity analyses instead of using penalty/correction to examine robustness of the data; and b) to provide a detailed description of the statistical analyses and imputation approach when submitting the SAP for this study.

6.1.2. Study Results

Compliance with Good Clinical Practices
The Applicant reports that this study was conducted in compliance with Good Clinical Practices.

Financial Disclosure
No new information on financial disclosure was provided in the NDA resubmission.

Patient Disposition
From the total of 359 patients screened, 241 patients were enrolled in the run-in-period and 219 patients were randomized to either Process V or Process VI, as depicted in the flowchart below (Figure 3). Overall, 205 patients (93.6%) completed the study with a balanced number of completers between the Process V and Process VI treatment groups.

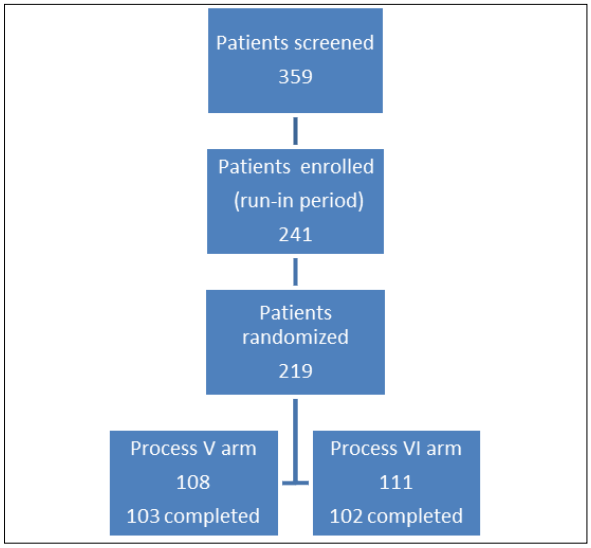

Figure 3: Study MYL-1501D-3004 patient disposition
Source: Diagram created by the Clinical Reviewer from data reported in the Clinical Study Report (CSR) file.

Patient population definitions
Intent-to-treat (ITT) population: All patients randomized to receive treatment (identical to the randomized population).
Safety population: All randomized patients who received at least one dose of IP
Per-protocol (PP) population: All patients who completed Week 18 and had HbA1c measurements per the protocol or had at least 1 post-baseline HbA1c data point for patients who discontinued prematurely and did not have protocol deviation that impacted the primary outcome. Patients who met rescue medication criteria and took rescue medication were excluded from the PP population.

The majority of screen failures was reported to patients who did not meet the inclusion criteria (103 of 118). From the 241 patients who entered the run-in period, there were 23 run-in failures with the higher proportion due to withdrawals (8 patients) and lost to follow-up (7 patients). One female patient (number (b) (6)) randomized to the Process VI arm was excluded from the safety population analysis because this patient developed an SAE of diabetic ketoacidosis (DKA) before starting treatment and withdrew the informed consent. This patient was counted as a run-in failure and also as treatment discontinuation due to an SAE of DKA. While this patient was included in the ITT population, she did not meet the criteria for inclusion in the safety population because she did not receive any study medication.

The most common reason for discontinuation from the investigational product (IP) was consent withdrawal (total of 8 patients, 3.7%). While the reasons for consent withdrawal are unclear, the number of patients who withdrew consent are similar between the two groups. One patient in the Process VI group discontinued due to an AE of grade 1 hyperglycemia. The

reasons for discontinuation are summarized per treatment group in Table 4.

Table 4: Reasons for IP discontinuation (ITT population)

Reason for discontinuation	Process V (N=108) n (%)	Process VI (N=111) n (%)
Withdrawal of consent	3 (2.8%)	5 (4.5%)
Protocol deviation	0	1 (0.9%)
Adverse event	0	1 (0.9%)
Lost to follow-up	1 (0.9%)	1 (0.9%)
Patient did not receive IP	0	1 (0.9%)

IP: Investigational product; ITT: intent-to-treat
Source: Table created by the Clinical Reviewer from data included in Figure 2 (Subject Disposition) of CSR file.

Protocol Violations/Deviations

Protocol violations were classified as major (28 cases) and minor violations (173 cases) and the reported percentages of protocol violations are similar for Process V and Process VI groups. The number of patients reported with protocol violations per group is listed in Table 5.

Table 5: Major and minor protocol deviations reported during the treatment period

PROTOCOL DEVIATIONS	Process V (N=108) n (%)	Process VI (N=111) n (%)
Major Protocol Deviation	15 (13.9)	13 (11.7)
Concomitant medication criteria	5 (4.6)	3 (2.7)
Laboratory assessment criteria	2 (1.9)	3 (2.7)
Informed consent	2 (1.9)	2 (1.8)
Visit schedule criteria	3 (2.8)	1 (0.9)
Serious adverse event criteria	1 (0.9)	2 (1.8)
Study procedures criteria	2 (1.9)	1 (0.9)
IP compliance	1 (0.9)	1 (0.9)
Eligibility and entry criteria	0	1 (0.9)
Minor Protocol Deviation	88 (81.5)	85 (76.6)
Study procedures criteria	76 (70.4)	73 (65.8)
Visit schedule criteria	13 (12.0)	17 (15.3)
IP compliance	11 (10.2)	12 (10.8)
Other criteria	9 (8.3)	8 (7.2)
Laboratory assessment criteria	7 (6.5)	5 (4.5)
Concomitant medication criteria	5 (4.6)	4 (3.6)
Source document criteria	2 (1.9)	0

IP: Investigational product
Source: Table adapted by the Clinical Reviewer from Table 14.1.2.3, CSR.

Demographic Characteristics of the ITT Population

All patients randomized were included in the ITT population. As explained above, one patient out of the 111 patients randomized to Process VI developed DKA and withdrew consent prior to receiving any dose of IP. The Clinical Reviewer recreated the demographics table using the ITT

population and the datasets provided in the NDA application (Table 6). The numbers in Table 6 compared to those in the table provided by the Applicant (Table 6, CSR, page 49) are identical, except for slightly different percentages in the category 'Ethnicity' (subcategory 'Hispanic or Latino' and 'Not Hispanic or Latino') that appear to be due to minor calculation errors in the CSR table. These minor calculation errors do not result in any changes in interpretation of the data.

In summary, the ITT population was comprised of: twice as many males than females, mean age of 43 years, predominantly White (not Hispanic or Latino). The overall demographic characteristics of the ITT population were balanced between patients randomized to Process V and to Process VI product.

Table 6: Demographic characteristics of the primary efficacy analysis (ITT population)

Subgroup	MYL-1501D Process V (N = 108)	MYL-1501D Process VI (N = 111)
Gender n (%)		
Female	36 (33.3)	35 (31.5)
Male	72 (66.7)	76 (68.5)
Age (years)		
Mean	42.71	42.84
Standard Deviation	11.46	12.14
Minimum, Maximum	19, 65	18, 65
Median	42	43
Age Group n (%)		
Age < 21 years	2 (1.9)	2 (1.8)
Age ≥21 and <65 years	104 (96.3)	107 (96.4)
Age > 65 years	2 (1.9)	2 (1.8)
Race n (%)		
American Indian or Alaska Native	1 (0.9)	1 (0.9)
Asian	6 (5.6)	2 (1.8)
Black or African American	6 (5.6)	5 (4.5)
White	95 (88.0)	103 (92.8)
Ethnicity n (%)		
Hispanic or Latino	7 (6.5)	11 (9.9)
Missing	3 (2.8)	2 (1.8)
Not Hispanic or Latino	98 (90.7)	98 (88.3)
HbA1c at baseline		
Mean	7.28	7.37
Standard Deviation	0.88	0.87
Minimum, Maximum	4.8, 9.3	5.2, 9.2
Median	7.3	7.4
BMI at screening (kg/m^2)		
Mean	27.37	27.29
Standard Deviation	3.73	3.93
Minimum, Maximum	20.3, 34.8	19.1, 35.3
Median	27.15	27
Duration of Diabetes (years)		
Mean	22.32	21.74
Standard Deviation	13.29	13.34
Minimum, Maximum	1.14, 52.1	1.14, 56.21
Median	19.77	19.2

Source: Table created by the Clinical Reviewer using the adsl.xpt dataset with the Demographic Tool V.3, FDA

Office of Computational Science (For comparison see Table 6, page 49 of CSR)

Other Baseline Characteristics

Baseline diabetes characteristics compared between the two treatment groups included the following: time of insulin glargine administration (morning or afternoon), baseline fasting plasma glucose, and fasting C-peptide. In summary, randomized patients had a baseline fasting plasma glucose (FPG) of approximately 9 mmol/L (162 mg/dL), and fasting C-peptide of 0.04 µmol/L. All patients were on insulin use prior to screening, and about 75% of the patients were administering insulin glargine at the evening time. The medical history of patients presents a similar profile between the two groups. All baseline diabetes characteristics were comparable between the Process V and Process VI treatment groups. The data submitted by the Applicant were replicated by the Clinical Reviewer with no disparities.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance: Treatment accountability and compliance were assessed at Weeks 2, 6, 12, 15 and 18. In the safety population, there were 11 patients (10.2%) in Process V and 6 patients (5.5%) in Process VI group with IP non-compliance. Non-compliance included: missing total mealtime insulin, missing basal insulin daily, taking 2-times more basal insulin daily; and taking less or more than prescribed basal insulin dose units daily. While there was a numerical imbalance in non-compliance numbers between treatment groups, it is unlikely that this imbalance has influenced the safety results.

Concomitant Medications: There is no noticeable imbalance in concomitant medications used during the treatment period between Process V and Process VI groups that could account for differences in efficacy or safety due to drug-drug interactions. A table was generated by the Clinical Reviewer of concomitant medications categorized by medication class used during the treatment period by more than 5% of the patients in any group (See Table 7).

Table 7: Most common concomitant medication class used during the treatment period

Medication Class	MYL-1501D Process V N=108	MYL-1501D Process VI N=110
Insulins and analogues for injection, long-acting	108 (100.0%)	110 (100.0%)
Insulins and analogues for injection, fast-acting	107 (99.1%)	108 (98.2%)
HMG-CoA reductase inhibitors	34 (31.5%)	36 (32.7%)
ACE inhibitors, plain	25 (23.1%)	27 (24.5%)
Propionic acid derivatives	17 (15.7%)	24 (21.8%)
Thyroid hormones	18 (16.7%)	18 (16.4%)
Anilides	13 (12.0%)	14 (12.7%)
Vitamin D and analogues	14 (13.0%)	13 (11.8%)
Insulins and analogues for injection, intermediate-acting	14 (13.0%)	10 (9.1%)
Platelet aggregation inhibitors excl. Heparin	11 (10.2%)	12 (10.9%)
Multivitamins, plain	5 (4.6%)	14 (12.7%)
Proton pump inhibitors	6 (5.6%)	10 (9.1%)
Other antihistamines for systemic use	6 (5.6%)	9 (8.2%)
Angiotensin II antagonists, plain	10 (9.3%)	4 (3.6%)
Other antidepressants	4 (3.7%)	9 (8.2%)
Selective serotonin re-uptake inhibitors	7 (6.5%)	6 (5.5%)
Piperazine derivatives	7 (6.5%)	6 (5.5%)
Glycogenolytic hormones	7 (6.5%)	6 (5.5%)
Other analgesics and antipyretics	3 (2.8%)	9 (8.2%)

Source: Table generated by Clinical Reviewer using the datasets provided and JReview tool.

Rescue Medication Use: Rescue criterion was defined for hyperglycemia as increase of >1% in HbA1c measurement at Week 12 compared to baseline value. This criterion was used to identify potential worsening of glucose control and to modify therapy at the discretion of the Investigator. Patients who received rescue medication were excluded from the PP population analyses. The Applicant reported 7 patients in Process V group and 3 patients in Process VI group who received rescue medication due to increase >1% in HbA1c from baseline at Week 12. The rescue medication used and described in the CSR is Lantus.

Efficacy Results

This section contains a summary of the efficacy results. For a complete review of efficacy, please refer to the statistical review performed by Dr. Anna Ketterman.

The original 505(b)(2) application for MYL-1501D (Semglee) was submitted on 04/27/2017 with two Phase 3 studies (MYL-1501D-3001 and MYL-1501D-3002) to support non-inferiority of MYL-1501D to the reference product Lantus. The major manufacturing changes between the product used in clinical trials (Process V) and the to-be-marketed product (Process VI) were

cited as a deficiency in the CR Letter. To resolve this deficiency, the Applicant conducted a clinical bridging study (MYL-1501D-3004) between Process V and Process VI to allow for reliance on studies performed with Process V to establish similarity between Process VI (to-be-marketed product) and Lantus.

Primary Endpoint

Study 3001 (in patients with T1DM) and Study 3002 (in patients with T2DM) analyzed in the original NDA submission, demonstrated non-inferiority (pre-defined margin 0.4%) of MYL-1501D to Lantus based on change in HbA1c at Week 24 from baseline (Table 8).

Table 8: Results of the primary efficacy endpoint analysis for Study 3001 and Study 3002

	Process V	Lantus
Study 3001 (T1DM)	N=280	N=278
Change in HbA1c at Week 24 from baseline, adjusted mean	0.11	0.08
Difference in change (Process V – Lantus), adjusted mean (95% CI)	0.03 (-0.06, 0.12)	
Study 3002 (T2DM)	N=277	N=283
Change in HbA1c at Week 24 from baseline, adjusted mean	-0.37	-0.42
Difference in change (Process V – Lantus), adjusted mean (95% CI)	0.05 (-0.11, 0.21)	

Source: Excerpted from the Statistical review performed by Dr. Ketterman checked in DARRTS on 04/16/2018

The similarity between Process VI (to-be-marketed product) to Process V was demonstrated in the bridging study (Study 3004). The result of efficacy analysis met the pre-defined difference margin (no greater than 0.4%) between Process VI and Process V products, demonstrated by the upper limit of the 2-sided 95% CI (0.1%) for the difference in change in HbA1c at Week 18 from baseline (Table 9).

Table 9: Results of the primary efficacy endpoint analysis for Study 3004

HbA1c	Process VI	Process V
Change in HbA1c (%) at Week-18 from baseline, adjusted mean (95% CI)	0.14(0.05, 0.24)	0.18(0.08, 0.28)
Difference in change (%) between Process VI and V, adjusted mean (95% CI)	-0.04 (-0.18, 0.1)	

Analysis using Return to Baseline Imputation Approach (including post-rescue HbA1c values)
Source: Excerpted from Statistical Review performed by Dr. Ketterman, (Table 6, page 12)

Mylan's imputation approach did not include post-rescue HbA1c values and the results differed slightly from the findings of the Statistical Reviewer: change in HbA1c at Week 18 from baseline (95% CI) was 0.18 (0.076, 0.290) for Process V and 0.15 (0.049, 0.255) for Process VI, with a mean difference (95% CI) in HbA1c of -0.03 (-0.171, 0.110). However, the difference in findings between the Statistical Reviewer and the Applicant does not change the overall conclusion of the analysis and support the similarity between Process V and Process VI.

Robustness of the HbA1c findings was tested by the Statistical Reviewer by performing a 1-way tipping point analysis, where the penalty values were added only to the imputed missing values for subjects in Process VI arm. The tipping point analysis resulted in a penalty of 1.9% or more to reverse the conclusion of non-inferiority between Process VI and Lantus, using the upper 95% CI of 0.12% for the difference in mean change in HbA1c between Process V and Lantus. The results of the tipping point analysis demonstrated that it would take impractical circumstances to tip the results from Process VI being non-inferior to Lantus.

Change in HbA1c overtime: The mean HbA1c levels measured at Week 12 and Week 18 did not show significant changes relative to the mean baseline level for each treatment group. While this was a relatively short study and there are only two post-baseline measurements, in the graph shown by the Applicant, the profile of HbA1c change over time for Process V and Process VI are practically overlapping (see Figure 4).

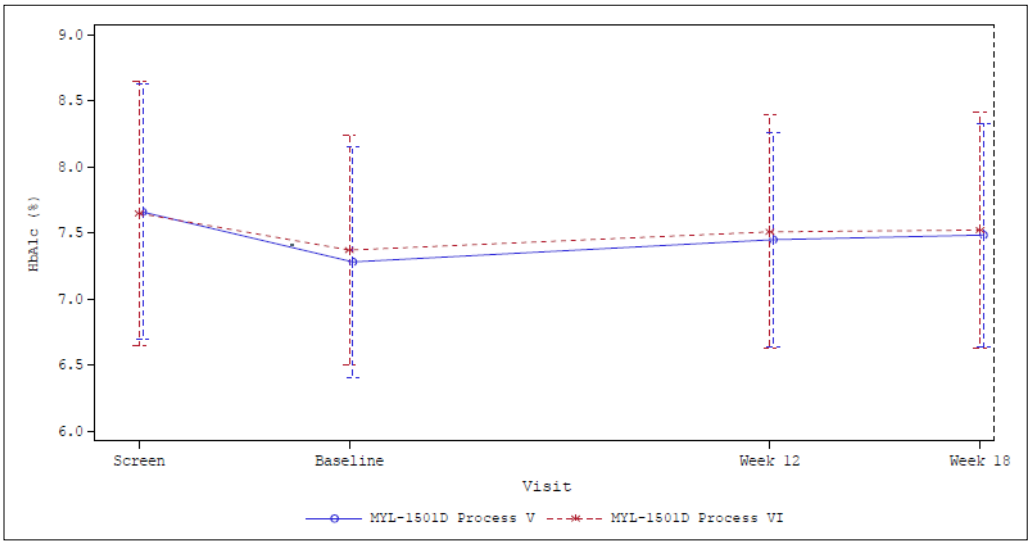

Figure 4: Mean ± SD of HbA1c (%) over time by treatment using multiple imputation (ITT population)
Vertical lines at visits indicate the Mean ± SD. Missing data were imputed using a multiple imputation method.
Source: Excerpted from Figure 4, CSR.

Data Quality and Integrity
The Applicant provided audit certificates, documentation of inter-laboratory standardization methods and quality assurance procedures. Overall, data quality and integrity appear adequate to support a clinical review.

Efficacy Results – Secondary and other relevant endpoints

- Fasting plasma glucose (FPG) remained relatively stable from baseline in both treatment groups and no statistically treatment differences were observed at any time point. The

similarity between Process V and Process VI in FPG was confirmed by the Statistical Reviewer's findings. The mean values of actual FPG measurements over time presented by the Applicant are illustrated in Figure 5.

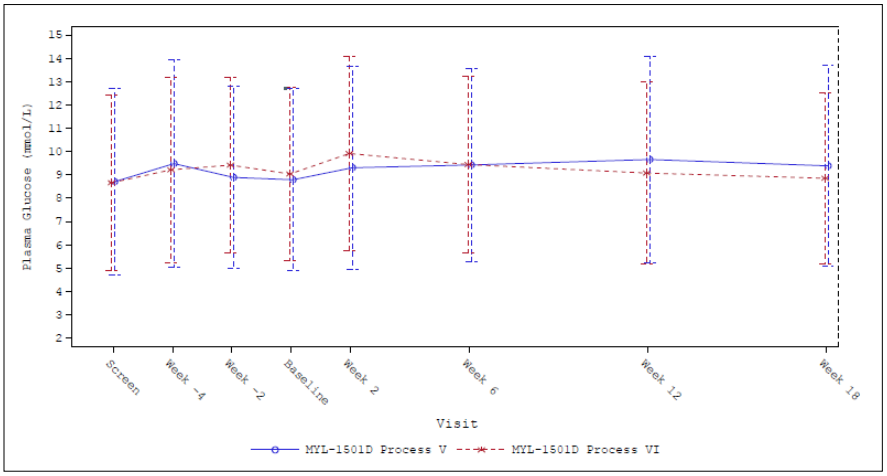

Figure 5: Mean ± SD of the actual FPG by visit and by treatment
Source: Excerpted from Figure 5, CSR

- There were no statistically significant differences between treatment groups in daily basal, mealtime or total daily insulin dose reported by the Applicant. The mean values of actual basal insulin dose over time is illustrated in Figure 6 and the mean values of actual total insulin dose are illustrated in Figure 7.

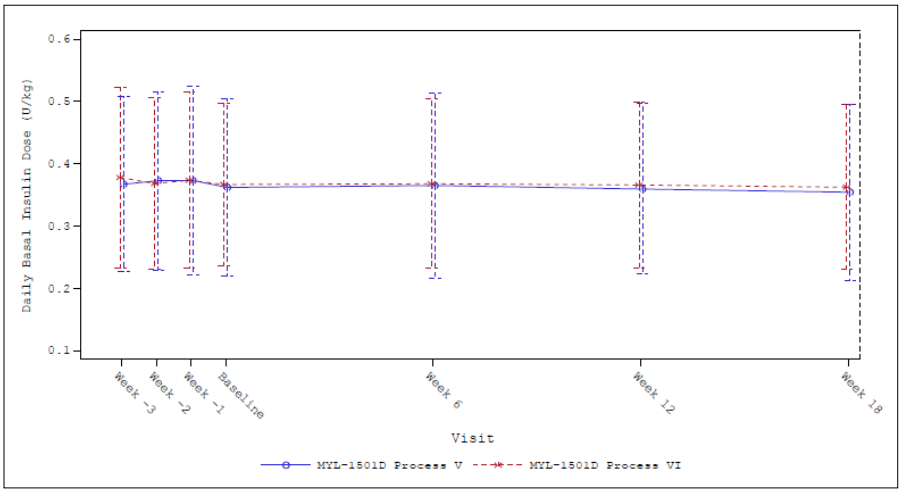

Figure 6: Mean ± SD of the actual daily basal insulin dose by visit and treatment
Source: Excerpted from Figure 6, CSR.

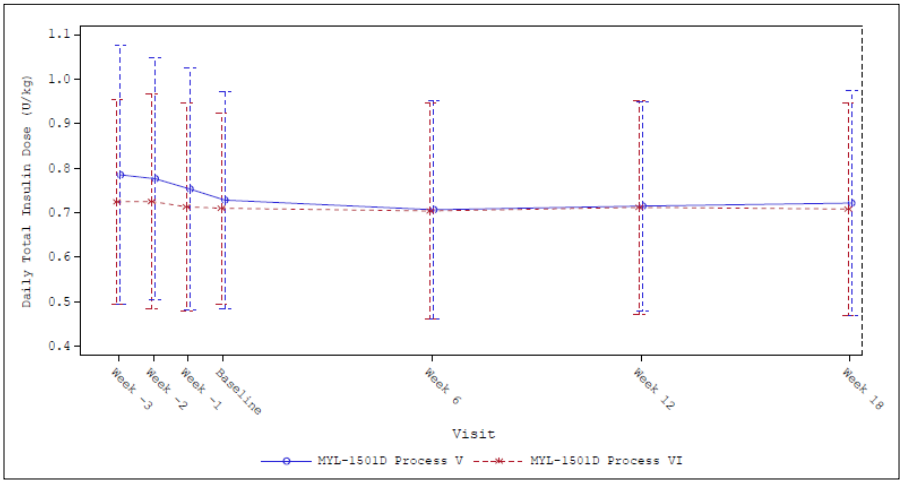

Figure 7: Mean ± SD of the actual total daily insulin dose by visit and treatment
Source: Excerpted from Figure 8, CSR

- The SMBG profiles were similar in both treatment groups, and no statistically significant differences were observed in SMBG changes from baseline over time between the two treatment groups.

In conclusion, the results of efficacy analysis demonstrate that the primary and secondary efficacy endpoints of Study MYL-1501D-3004 were met.

Pharmacokinetic (PK) Results: PK data in this study were collected for exploratory analyses, and descriptive statistics of PK data were presented by visit in each treatment group. No statistically significant differences were observed in PK profiles between Process V and Process VI groups. The geometric LS mean concentration ranged from 0.362 ng/mL to 0.406 ng/mL in the Process V group and from 0.355 ng/mL to 0.382 ng/mL in the Process VI group. After evaluating the PK data, the Clinical Pharmacology Reviewer concluded that the range of M1 trough concentrations were in general comparable between process VI and Process V treatment arms. These observations were consistent with the PK comparability results observed in the dedicated PK/PD studies 1003 and 1001.

Dose/Dose Response
The dose of the Process V and Process VI basal insulin were adjusted individually. No drug concentration information or dose response data were collected in this study.

Durability of Response
No data on durability of response were collected in this study.

Persistence of Effect
Persistence of effect was not assessed in this study.

Additional Analyses Conducted on the Individual Trial
No additional analyses were conducted on the individual trial.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable. This application consists of a single clinical trial (MYL-1501D-3004).

7.1.1. Primary Endpoints

See Study Endpoints in Section 6.1.1.

7.1.2. Secondary and Other Endpoints

See Study Endpoints in Section 6.1.1.

7.1.3. Subpopulations

Change from baseline in HbA1c over time analyzed by age, gender, race and ethnicity subgroups was similar between treatment groups. Results of the subgroup analysis of changes from baseline in HbA1c over time comparing Process VI to Process V by treatment differences at Wek 18 are summarized in Table 10.

Table 10: Change from baseline in HbA1c over time comparing Process VI to Process V treatment groups (Relative Difference and Confidence Interval)

	RD	95% CI	p-value
Gender			
Female	-0.11	-0.281, 0.060	0.203
Male	0.08	-0.200, 0.355	0.578
Age[1]			
>21 and <65 years	-0.05	-0.186, 0.095	0.521
Race			
White	-0.05	-0.197, 0.094	0.485
All others	-0.17	-0.749, 0.409	0.516
Ethnicity[2]			
Not Hispanic or Latino	-0.04	-0.192, 0.108	0.584

RD: Relative difference between Process VI and Process V.
[1] Not calculated for other age subgroups due to low number of patients
[2] Not calculated for Hispanic or Latino due to low number of patients
Source: Table created by Clinical Reviewer with data provided in Section 11.4.1.1.3, CSR

As shown in Table 10, no statistically significant differences between the two treatment groups were appreciated in any of the subgroups analyzed. The consistency of treatment effects across subgroups and with overall treatment effect was tested and confirmed by the Statistical Reviewer.

7.1.4. Dose and Dose-Response

See Section 6.1.2.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See Section 6.1.2.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The original NDA submission was supported by clinical trials in patients with T1DM (Study 3001) and T2DM (Study 3002) using the Process V product manufactured in India to demonstrated efficacy and safety similarity to the RLD Lantus. Since the manufacturing facility was changed from India to Malaysia for the production of the to-be-marketed product (Process VI), Study MYL-1501D-3004 was conducted to provide a safety and efficacy bridge between Process V and Process VI. The overall efficacy and safety results from Study MYL-1501D-3004 are consistent with similarity between Process VI and Process V, thus supporting reliance on studies with Process V and Lantus to establish similarity between Process VI and Lantus.

7.2.2. Other Relevant Benefits

Please refer to the review of the original NDA Application.

7.3. Integrated Assessment of Effectiveness

Please refer to the review of the original NDA Application.

8. Review of Safety

8.1. Safety Review Approach

The review of safety in this NDA re-submission is focused on the safety database of the Study MYL-1501D-3004, which was designed to compare the safety between MYL-1501D Process V and MYL-1501D Process VI. The safety endpoints assessed in Study MYL-1501D-3004 are discussed in detail in separate Review Sub-sections as listed in Table 11.

Table 11: List of sub-sections for detailed discussion of safety endpoints

Safety endpoint	Review Sub-section number
Incidence of positive antibody response and change in antibody percentage binding from baseline	8.4.10
Change in hypoglycemia rate (30-day adjusted) from baseline and incidence of hypoglycemic events	8.5.1
Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)	8.4.1, 8.4.2 and 8.4.5
Incidence of local reactions, systemic reactions and other AEs	8.4.4 and 8.4.5
Incidence of device-related complaint/problems	4.6 and 8.4.5

Source: Table compiled by the Clinical Reviewer with links to detailed discussion for the safety endpoints listed

Safety assessments conducted for Study MYL-1501D-3004 and reviewed in this NDA re-submission included: physical examination, vital signs, 12-lead ECG, clinical laboratory analyses, immunogenicity, and incidence of AEs and of hypoglycemic events. Concomitant medications and records of device safety information were also assessed during the study period. In-person or telephone visits were schedule at Week 0 (baseline) and Weeks 1, 2, 4, 6, 9, 12, 15, and 18 (end of trial) with a follow-up visit scheduled at Week 20. Visits at Weeks 1, 4, and 9 were telephone contacts.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety population was defined as all patients who were randomized and received ≥1 dose of IP and included 218 patients. The duration of exposure to study drug (in mean±SD) was similar between the groups: 123.9±17.06 days for Process V group (n=108) and 123.4±18.28 days for Process VI group (n=109). One patient (# 4006104) from Process VI was missing exposure duration due to unknown date of last dose.

No statistically significant differences were noted between treatment groups in exposure to daily mealtime insulin, daily basal insulin or daily total insulin doses measured as mean change from baseline at Week 6, Week 12 and Week 18. See discussion on insulin dose in Section 6.1.2.

Relevant characteristics of the safety population: No meaningful differences between treatment groups were observed in the incidence of TEAEs by population subgroups. A wide CI variation is observed for certain subgroups due to a small number of patients in that subgroup, e.g., Asian and African American race groups (Table 12).

Table 12: Characteristics of the Safety Population in Process V and Process VI treatment groups – Incidence of TEAEs sub subgroups.

Safety Population	Process V		Process VI		Relative Risk	Risk Difference
	n (%)	N	n (%)	N	RR (95% CI)	RD (95% CI)
Treatment Emergent subgroup	45 (41.7)	108	46 (41.8)	110	1 (0.73, 1.37)	0.15 (-12.94, 13.24)
Sex						
Female	12 (33.3)	36	19 (55.9)	34	1.68 (0.97, 2.91)	22.55 (-0.16, 45.26)
Male	33 (45.8)	72	27 (35.5)	76	0.78 (0.52, 1.15)	-10.31 (-26.06, 5.45)
Age Group						
Age <21 years	0	2	1 (50.0)	2	3 (0.19, 47.96)	50 (-19.3, 119.3)
Age >21 and <65 years	44 (42.3)	104	43 (40.6)	106	0.96 (0.7, 1.32)	-1.74 (-15.07, 11.58)
Age >65 years	1 (50.0)	2	2 (100)	2	1.67 (0.48, 5.76)	50 (-19.3, 119.3)
Race						
American Indian or Alaska Native	0	1	0	1	1 (0.03, 29.81)	0 (0, 0)
Asian	2 (33.3)	6	1 (50.0)	2	1.5 (0.25, 8.98)	16.67 (-62.23, 95.56)
Black or African American	2 (33.3)	6	1 (20.0)	5	0.6 (0.07, 4.83)	-13.33 (-64.83, 38.16)
White	41 (43.2)	95	44 (43.1)	102	1 (0.73, 1.38)	-0.02 (-13.86, 13.82)
Ethnicity						
Hispanic or Latino	2 (28.6)	7	3 (27.3)	11	0.95 (0.21, 4.35)	-1.3 (-43.87, 41.28)
Missing	2 (66.7)	3	1 (50.0)	2	0.75 (0.15, 3.72)	-16.67 (-104.12, 70.78)
Not Hispanic or Latino	41 (41.8)	98	42 (43.3)	97	1.03 (0.75, 1.43)	1.46 (-12.42, 15.34)

Source: Table created by the Clinical Reviewer using the Demographic Analysis Tool, Office of Computational Science (OCS), FDA

8.2.2. Adequacy of the safety database:

The safety database submitted is adequate for conducting a clinical review.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity and submission quality were identified in this NDA submission.

8.3.2. Categorization of Adverse Events

The categorization of adverse events in SAEs and TEAEs followed the standard criteria. AEs were also classified by severity following the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03 grading criteria (Table 13).

Table 13: Adverse Event Clinical Severity Grading Criteria

Clinical Severity Grading		
Grade 1	MILD	Does not interfere with subject's usual function.
Grade 2	MODERATE	Interferes to some extent with subject's usual function.
Grade 3	SEVERE	Interferes significantly with subject's usual function.
Grade 4	LIFE-THREATENING	Risk of death at time of event
Grade 5	DEATH	Death related to AE

Clinical severity grading of adverse events according to NCI-CTCAE Criteria Version 4.03.
Source: Excerpted from Table 5, Protocol, Version 2.0

All AEs were coded by MedDRA terms, Version 21.0. The Applicant provided summaries of TEAEs by severity, relationship to IP, TEAEs leading to discontinuation, SAEs, systemic and local allergic reactions, and device-related assessments.

8.3.3. Routine Clinical Tests

Routine clinical tests included hematology, chemistry, renal and liver function tests, lipid profile and urinalysis.

8.4. Safety Results

8.4.1. Deaths

No deaths were reported in this trial.

8.4.2. Serious Adverse Events

The Applicant defined serious adverse events (SAEs) using the regulatory specified criteria for designation of seriousness and included an intensity criteria, *i.e.*, AEs that met criteria for severity grade 4 and grade 5 according to NCI-CTCAE grading criteria (see Table 13). SAEs included all severe hypoglycemia, *i.e.*, hypoglycemic events requiring third party assistance. All 3 SAEs reported in the Process V were severe hypoglycemic events. In the Process VI group, the total of 7 SAEs experienced during treatment period included 4 events of severe hypoglycemia, 1 finger laceration, 1 food allergy and 1 diabetic ketoacidosis.

The patient (ID (b) (6)) who developed ketoacidosis while receiving MYL-1501D Process VI, was a 55-year old female with a 9-year history of T1DM and several diabetic and non-diabetic complications. On Day 93 of treatment, the patient was reported with non-serious epigastric pain, nausea and vomiting and stopped both, the Humalog and the study medication. She did not measure the blood glucose and on Day 95 she presented to her primary care physician who suspected stomach flu and sent the patient to the emergency room, where she was diagnosed with Grade 3 DKA and hospitalized. At admission, the patient had betahydroxybutirate level of 58.1 mg/dL (reference range <2.8 mg/dL), bicarbonate of 13 mEq/L (reference range 23 – 27 mEq/L) and glucose of 468 mg/dL. In addition, the patient was reported with pyuria, Grade 2 acute kidney injury, and hypertension. On Day 97, the event of DKA was considered resolved, the patient was discharged home, and administration of the study medication was resumed. Both, the Investigator and the Applicant assessed the DKA event as not related to the study medication and based on the narrative provided, I concur with their assessment.

The incidence of treatment-emergent SAEs by System Organ Class (SOC) and Preferred Term (PT) is summarized in Table 14. For severe hypoglycemic events, please see discussion on Hypoglycemia in Section 8.5.1.

Table 14: SAEs reported by SOC and PT (number of patients and number of events) during treatment period in Process V and Process VI groups

System Organ Class Preferred Term	Process V N=108		Process VI N=110		p-value
	n (%)	events	n (%)	events	
Any SOC	3 (2.8)	4	7 (6.4)	7	0.332
Immune System Disorders	0		1 (0.9)	1	1.0
Food allergy	0		1 (0.9)	1	1.0
Injury, Poisoning and Procedural Complications	0		1 (0.9)	1	1.0
Laceration	0		1 (0.9)	1	1.0
Metabolism and Nutrition Disorders	3 (2.8)	4	5 (4.5)	5	0.722
Hypoglycemia	3 (2.8)	4	4 (3.6)	4	1.0
Diabetic ketoacidosis	0		1 (0.9)	1	1.0

SOC and PT coded by MedDRA version 21.0
Source: Adapted by Clinical Reviewer from Table 21, CSR

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

A single patient (ID (b) (6)) was reported for treatment discontinuation. The patient was a 30-year-old female from Process VI group and the reason for discontinuation was an AE of Grade 1 hyperglycemia. However, no blood glucose at the time of the event is available. The patient had a screening glucose level of 79 mg/dL and a baseline (Week 0) of 108 mg/dL. On Day 2, the patient experienced symptoms of abdominal pain (stomach cramp), increased appetite, dizziness, and headache. The last administration of study drug was on Day 5. The

symptoms persisted and on Day 8 the patient experienced also nausea and ketosis, which resolved on the following day. On Day 11, the blood glucose level was 232 mg/dL and the patient was discontinued from the study. While the event of hyperglycemia was assessed by the Investigator as possibly related to the IP, the information provided is insufficient to assess relatedness of this event to the IP. It is unclear why the IP administration was not resumed after the event resolved. This was a single case of discontinuation due to adverse events, had no serious outcome and does not appear to contribute to a safety imbalance between treatment arms.

8.4.4. Significant Adverse Events

The Applicant considered as significant adverse events: Local or systemic allergic reactions and TEAEs that led to discontinuation of the IP.

Local/systemic allergic reactions: There was a single patient (ID (b) (6)) reporting a local reaction (Grade 1 injection site hemorrhage) in the Process VI group, on Day 6 of treatment. While this event was reported as a TEAE under the category of local/systemic allergic events (see Section 8.4.5, Table 12), the TEAE was considered by the Investigator as unrelated to the IP and rather related to the insulin glargine needle. The AE resolved in the following day and no further information was provided on this case.

IP Discontinuation: There was one patient (ID (b) (6)) in the Process VI group with IP discontinuation due to hyperglycemia (See discussion on Discontinuation, Section 8.4.3). No other TEAE was reported as cause for IP discontinuation.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The overall number of patients reported with AEs and TEAEs as well as the respective number of events are similar between the Process V and Process VI groups, as shown in Table 15. The number of AEs includes events reported during the whole study period, i.e., screening, run-in, and treatment periods, while the number of TEAEs reflect the number of events reported during the period when the patients received IP. It is noted that only severe hypoglycemic events were reported in the AE/TEAE case report forms (CRFs) as SAEs, while all hypoglycemic events (including severe hypoglycemia) where reported in a dedicated Hypoglycemia CRF. The numbers reported by the Applicant were replicated by the Clinical Reviewer using the JReview analysis tool and are summarized in Table 15.

Table 15: **Summary of Adverse Events**

Category[a]	Process V N=108		Process VI N=110		
	n (%)	e	n (%)	e	p-value[b]
Subjects with **≥1** AE[c]	56 (51.9)	119	64 (58.2)	155	0.348
Subjects with **≥1** TEAE	45 (41.7)	85	46 (41.8)	106	0.982
Subjects with **≥** 1 SAE	3 (2.8)	4	7 (6.4)	7	0.332
Subjects with treatment-related SAE[d]	1 (0.9)	1	1 (0.9)	1	1.000
Subjects with **≥1** Grade **≥** 3 TEAE	4 (3.7)	9	8 (7.3)	8	0.248
Subjects with treatment-related TEAE	1 (0.9)	1	6 (5.5)	13	0.119
Subjects who discontinued study medication due to AE	0	0	1 (0.9)	1	1.000
Subjects with **≥** 1 TEAE related to insulin glargine pen/needle	0	0	3 (2.7)	9	0.247
Subjects with **≥1** TEAE of local or systemic allergic reaction	0	0	1 (0.9)[c]	1	1.000

AE: adverse event; TEAE: treatment-emergent AE; SAE: serious AE; e: number of events
a Multiple occurrences of the same AE/TEAE in one individual are counted only once.
b p-value was computed from Chi-square test if 80% of the cells have an expected frequency ≥5, Fisher's exact test was used otherwise.
c AEs reported during the whole study period including screening, run-in, and treatment periods
d Subject (b) (6) experienced injection site hemorrhage, which was mapped to local allergic reactions.
Source: Adapted from Table 17, CSR.

While the overall incidence of TEAEs was similar between the Process V and Process VI groups, a numerical imbalance between groups was observed within certain categories of TEAEs with unfavorable results for Process VI. The number of events reported in each of these categories was small and the differences between Process V and Process VI groups were not statistically significant. However, to determine the clinical significance of these differences, a break-down of SAEs by SOC and PT was reviewed for the following TEAE categories:

a) Subjects with ≥1 SAEs: Severe hypoglycemia was the most common SAE reported and the incidence in the Process V group (3 subjects, 4 events) was similar to that of the Process VI group (4 patients, 4 events). An additional 3 events were reported in the Process VI group (see Table 16). A review of the narratives provided for the cases of food allergy and finger laceration is consistent with SAEs unrelated to the IP. There was a single case of DKA reported by a patient who interrupted insulin because of gastrointestinal symptoms that persisted for a few days, and the IP administration was resumed (see further details in Section 8.4.2).

Table 16: Number of patients and events reported with treatment-emergent SAEs, by SOC and PT

SAEs System Organ Class Preferred Term	Process V N=108		Process VI N=110	
	n (%)	e	n (%)	e
Any SOC	3 (2.8)	4	7 (6.4)	7
Immune System Disorders	0		1 (0.9)	1
Food allergy	0		1 (0.9)	1
Injury, Poisoning and Procedural Complications	0		1 (0.9)	1
Laceration	0		1 (0.9)	1
Metabolism and Nutrition Disorders	3 (2.8)	4	5 (4.5)	5
Hypoglycemia	3 (2.8)	4	4 (3.6)	4
Diabetic ketoacidosis	0		1 (0.9)	1

Source: Excerpted from Table 21, CSR

b) Subjects with ≥1 Grade ≥3 TEAEs: Since the criteria for AEs Grade ≥3 and for SAEs overlap, patients listed with AEs Grade ≥3 include all those reported with SAEs, as shown in Table 17. There was 1 patient in each treatment group with AEs Grade ≥3 who did not meet the criteria for SAEs.

Table 17: Incidence of Grade **≥3** TEAEs by SOC and PT

System Organ Class Preferred Term	Process V (N=108)	Process VI (N=110)
	n (%)	n (%)
Any SOC	4 (3.7)	8 (7.2)
Gastrointestinal Disorders	1 (0.9)	1 (0.9)
Nausea	1 (0.9)	0
Vomiting	1 (0.9)	0
Abdominal pain	0	1 (0.9)
Immune System Disorders	0	1 (0.9)
Food allergy	0	1 (0.9)
Infections and Infestations	0	1 (0.9)
Ear infection	0	1 (0.9)
Injury, Poisoning and Procedural Complications	0	1 (0.9)
Laceration	0	1 (0.9)
Metabolism and Nutrition Disorders	3 (2.8)	4 (3.6)
Hypoglycemia	3 (2.8)	3 (2.8)
Diabetic ketoacidosis	0	1 (0.9)
Musculoskeletal and Connective Tissue Disorders	1 (0.9)	0
Back pain	1 (0.9)	0
Pain in extremity	1 (0.9)	0
Arthralgia	1 (0.9)	0

Source: Excerpted from Table 20, CSR

c) Subjects with treatment-related TEAE: The Applicant defined treatment-related AE if in the

CRF the AE was marked as "possibly related", "probably related", or "definitively related". If the relationship information was missing, the AE was assumed to be "possibly related" to the study medication. There was a total of 6 treatment-related TEAEs reported for the Process VI group *vs*. 1 reported for the Process V group. To assess the clinical significance of the treatment-related TEAEs numerical imbalance, the AEs coded by both, SOC and PT were reviewed. As illustrated in Table 18, AEs coded by PT were associated with single reports and do not appear to map with any major target. In addition, two factors contributed to decrease my level of concern in this assessment: a) the inclusion of AEs missing relatedness determination and that may have inflated the number of events considered treatment-related; and b) the subjective determination of relatedness.

Table 18: Treatment-related TEAEs by system organ class and preferred term

System Organ Class Preferred Term	Process V (N=108) n (%)	Process VI (N=110) n (%)
Any SOC	1 (0.9)	6 (5.5%)
Eye Disorder	0	1 (0.9)
Vitreous hemorrhage	0	1 (0.9)
Gastrointestinal Disorders	0	1 (0.9)
Nausea	0	1 (0.9)
Abdominal pain upper	0	1 (0.9)
General Disorders and Administration Site Conditions	0	1 (0.9)
Injection site rash	0	1 (0.9)
Injury, Poisoning and Procedural Complications	0	1 (0.9)
Contusion	0	1 (0.9)
Investigations	0	1 (0.9)
Weight increased	0	1 (0.9)
Metabolism and Nutrition Disorders	1 (0.9)	2 (1.8)
Hypoglycemia	1 (0.9)	1 (0.9)
Ketosis	0	1 (0.9)
Hyperglycemia	0	1 (0.9)
Nervous System Disorders	0	1 (0.9)
Headache	0	1 (0.9)
Dizziness	0	1 (0.9)
Skin and Subcutaneous Disorders	0	2 (1.8)
Pain of skin	0	1 (0.9)
Pruritus	0	1 (0.9)

Treatment-related AE included AEs marked in the CRF as "possibly related", "probably related", or "definitively related". If the relationship information was missing, the AE was assumed to be "possibly related".
Source: Table 19, CSR

d) Subjects with ≥1 TEAE related to insulin glargine pen/needle: The Investigators reported TEAEs related to insulin glargine pen/needle for 3 patients (9 events) in the Process VI group *vs*. none in the Process V group. Each of the TEAEs reported was associated with a single patient, and except for the AE of 'pain of skin', which was reported by the verbatim

"stinging on the injection site", the remaining AEs do not appear to be directly related to insulin glargine pen/needle (Table 19). For the 2 remaining patients, details provided on event descriptions are consistent with malfunction of the pen injector, causing leakage or blockade of insulin during injection or errors in dialing the dose, ending up with higher or lower dose injected.

Table 19: TEAEs related to insulin glargine pen/needle by SOC (PT)

TEAEs related to insulin glargine pen/needle by SOC (PT)	Process V (N=108) n (%)/events	Process VI (N=110) n (%)/events
Any TEAEs	0	3 (2.7)/9
GI disorders (abdominal pain upper, nausea)	0	1 (0.9)/2
General disorders and administration site conditions (injection site hemorrhage)	0	1 (0.9)/1
Metabolism and nutrition disorders (hyperglycemia, increased appetite, ketosis)	0	1 (0.9)/3
Nervous system disorders (dizziness, headache)	0	1 (0.9)/2
Skin and subcutaneous tissue disorders (pain of skin)*	0	1 (0.9)/1

*The verbatim term used was "stinging on the injection site"
Source: Table 14.3.1.9.1

Incidence of common TEAEs in treatment groups
The most common TEAEs were in the SOC of Infections and Infestations, with similar percentage between treatment groups (21.3% in Process V and 19.1% in Process VI), followed by Gastrointestinal (GI) Disorders, and Metabolism and Nutrition Disorders. An imbalance (p=0.026) is noted between Process V and Process VI in the SOCs of GI Disorders and Metabolism and Nutrition Disorders. To evaluate the significance of this imbalance, the AEs were broken into PT categories (Table 20).

The most frequently reported AEs by PT in GI Disorders were diarrhea and nausea and while diarrhea was more frequent in Process V, nausea was more frequent in Process VI. However, the proportion of patients reporting these AEs was small and the difference between groups for these AEs was not statistically significant. Additional GI events reported that accounted for the difference between groups were abdominal pain, constipation, dyspepsia, gastroesophageal reflux and gingival swelling, each reported in no more than 2 patients in the Process VI group. It is noted that patients reported with AEs by the PT of gastroenteritis and gastroenteritis viral, under the SOC of Infections and Infestations could be associated with AEs reported under GI Disorders.

In the SOC of Metabolism and Nutrition Disorders, the most common reported AE by PT was hypoglycemia, with similar number of patients reporting this AE in the two treatment groups (see further discussion on hypoglycemia, in Section 8.5.1). The other AEs in the SOC of Metabolism and Nutrition Disorders include dyslipidemia, hyperlipidemia, hyperkalemia,

hyperglycemia, ketosis (1 event in each treatment group), and DKA (1 event in Process VI group; see further discussion on the DKA event in Section 8.4.2).

Table 20: Treatment-emergent adverse events by SOC and PT, selected for incidence of PT **≥2%** in any treatment group

System Organ Class Preferred Term	Process V N=108		Process VI N=110		p-value
	n (%)	e	n (%)	e	
Any System Organ Class	45 (41.7)	85	46 (41.8)	106	0.982
Infections and Infestations	23 (21.3)	26	21 (19.1)	26	0.685
Upper respiratory tract infection	7 (6.5)	7	3 (2.7)	3	0.213
Nasopharyngitis	4 (3.7)	4	4 (3.6)	4	1.000
Gastroenteritis	4 (3.7)	5	3 (2.7)	3	0.720
Gastroenteritis viral	0	0	4 (3.6)	4	0.122
Gastrointestinal Disorders	4 (3.7)	12	13 (11.8)	21	0.026
Diarrhea	4 (3.7)	5	2 (1.8)	2	0.443
Nausea	1 (0.9)	5	5 (4.5)	6	0.212
Metabolism and Nutrition Disorders	4 (3.7)	6	9 (8.2)	11	0.163
Hypoglycemia[a]	3 (2.8)	4	4 (3.6)	4	1.000

a Only severe hypoglycemic events were included in the AE-CRF; other hypoglycemias were reported in the Hypoglycemia CRF
e: number of events. AEs coded by MedDRA version 21.0
p-value was computed from Chi-square test if 80% of the cells have an expected frequency ≥5, Fisher's exact test was used otherwise.
Selected TEAEs with an incidence of ≥2% by PT in any treatment group, listed in descending order
Source: Excerpted from Table 18, CSR

Overall, the differences in the incidence of TEAEs between treatment groups were small and with no significant clinical impact to determine an imbalance in safety profile between Process V and Process VI.

8.4.6. Laboratory Findings

Clinical laboratory evaluations included chemistry and renal function, hematology, fasting lipid profile and urinalysis. There were no clinically meaningful changes in mean value of any laboratory parameters from baseline to Week 18 in any of the two treatment groups, and no statistically significant differences in mean change from baseline between the Process V and Process VI groups.

In clinical chemistry evaluations, markedly abnormal individual laboratory values were noted for low glucose (<55 mg/dL) and high glucose (>270 mg/dL) with similar proportions between the treatment groups (For further discussion on hypoglycemic events please refer to Section 8.5.1). Isolated cases of markedly abnormal values were noted for bilirubin [>2 x upper level of

normal (ULN)], alanine aminotransferase (ALT, >3 x ULN), aspartate aminotransferase (AST, >3 x ULN), and creatinine (>1.5 x ULN) as shown in Table 21.

Table 21: Number (percentage) of patients with markedly abnormal laboratory levels at baseline and Week 18 in Process V and Process VI groups.

Laboratory parameter	Process V		Process VI	
	Baseline n (%)	Week 18 n (%)	Baseline n (%)	Week 18 n (%)
Blood glucose				
< 55 mg/dL	6 (5.6%)	3 (2.8%)	3 (2.7%)	1 (0.9%)
>270 mg/dL	6 (5.6%)	10 (9.3%)	7 (6.4%)	6 (5.5%)
Bilirubin				
>2 x ULN	1 (0.9%)	0	0	0
Alanine aminotransferase (ALT)				
>3 x ULN	0	0	0	1 (0.9%)
Aspartate aminotransferase (AST)				
>3 x ULN	0	0	0	1 (0.9%)
Creatinine				
>1.5 x ULN	0	1 (0.9%)	1 (0.9%)	1 (0.9%)

ULN: Upper level of normal
Source: Table created by the Clinical Reviewer with data provided in the CSR, Table 14.3.4.2.4

The increase in ALT and AST (>3x ULN) mapped to a single patient (ID (b) (6)). The enzymes were increased at Week 18 and resolved in approximately 14 days. These changes in liver enzymes were determined by the Investigator as not related to the IP administration.

Overall, there was no clear evidence to indicate that the abnormal laboratory changes were associated with either Process V or Process VI products.

8.4.7. Vital Signs

Vital signs assessments included changes in mean vital sign parameters from baseline to Weeks 2, 6, 12 and 18 within each treatment group and between the two treatment groups. No clinically meaningful changes in vital sign values were noted overtime in any of the two treatment groups, and no clinically relevant treatment-related differences were noted in any vital sign.

The incidence of individual markedly abnormal vital sign values was compared between Process V and Process VI groups and was determined to be similar between the treatment groups.

8.4.8. Electrocardiograms (ECGs)

There were no reports of abnormal clinically significant ECG at baseline and no shifts from baseline to abnormal clinically significant ECG in either treatment group. The number of

patients with non-clinically significant ECG records at baseline and shifts from baseline was similar between groups.

8.4.9. QT

No QT evaluations were conducted in this trial.

8.4.10. Immunogenicity

This section contains a summary of the immunogenicity review performed by the Office of Biotechnology Products (OPB) in addition to my clinical assessment. Please refer to the OBP Review for complete information regarding immunogenicity.

A standard Radio-Immuno Precipitation Assay (RIPA) associated with a sample pre-treatment procedure (acid dissociation) was used for detection of anti-insulin antibodies (AIAs), and the presence of AIAs in the blood was measured by the formation of complex of antibody with insulin tracer and was expressed as % binding. The Office of Biotechnology Products (OPB) assessed the anti-drug antibody assay as suitable for the intended purpose.

Immunogenicity profiles of continuous variables (% specific binding) were analyzed using the MMRM method for each assay without imputing missing data and excluding the basal insulin dosing time. Immunogenicity profiles with binary outcomes (positive/negative) were summarized with frequency and percentage at scheduled visits for each assay. Comparison between treatment groups was assessed using Fisher's exact test, with p-value for 2-sided test. The relationship of insulin cross-reactive antibodies with HbA1c and insulin doses were analyzed by treatment group for each assay method. Treatment group difference was assessed by the incidence of patients with over 10% increase in cross reacting antibodies, with over 0.2% increase in HbA1c, and insulin dose increase at any visit.

The Applicant informed that the immunogenicity data was not available at the time of database lock for the analysis and were locked later. However, the information that the treatment remained blinded during the laboratory assay is reassuring to assume that data analysis was not biased. Overall, immunogenicity profiles, incidence of total insulin antibodies and cross-reactivity of insulin antibodies were comparable between the Process V and Process VI groups, as discussed below.

<u>Incidence of total and cross-reactive insulin antibody response</u>
The majority of patients in both treatment groups had positive response for total and cross-reactive AIAs. The percentage of patients with positive response for total insulin antibody was similar between the Process V and Process VI groups at both, baseline and Week 18. The incidence of cross-reactive insulin antibody response reflected the incidence of the total insulin antibody. See Table 22 for incidence rates of total insulin and cross-reactive insulin antibodies

at baseline and Week 18.

Table 22: Incidence rate of total and cross-reactive insulin antibody at baseline and Week 18 in Process V and Process VI groups.

Incidence rate	Process V		Process VI	
	Baseline	Week 18	Baseline	Week 18
Total insulin antibody	85.2%	86.1%	88.2%	86.3%
Cross-reactive insulin antibody	88.9%	86.1%	85.5%	84.3%

Source: Table created by the Clinical Reviewer with data provided in Section 12.5.3.3.1 of CSR

Total and cross-reactive insulin antibodies

The mean actual total and cross-reactive insulin antibody percent binding remained relatively stable from baseline to Week 18 in both, Process V and Process VI groups. No significant differences were noted in percent binding for total or cross-reactive insulin antibody by visit between treatment groups. Since the profile of total and cross-reactive insulin percent binding over time overlap, only the illustration of the actual cross-reactive insulin antibody percent binding over time is shown in Figure 8.

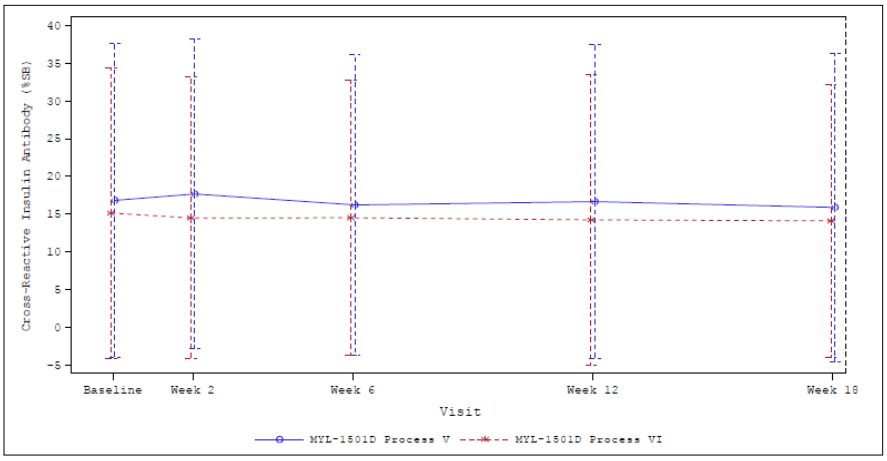

Figure 8: Actual cross-reactive insulin antibody percent binding over time by treatment (mean ± SD)

%SB: percent specific binding; SD: standard deviation; blue line: Process V; red line: Process VI.
Source: Excerpted from Figure 14, CSR

Anti-insulin antibody response subgroup analyses

While the study was not designed to detect treatment differences with high statistical power within subgroups, the subgroup analysis by gender, age and race of the actual and change from baseline in cross-reactive insulin antibody percent binding by visit showed similar results between the Process V and Process VI groups.

Hypersensitivity and severe hypoglycemic events associated with cross-reactive antibodies

Patients with cross-reactive antibody were analyzed for the incidence of hypersensitivity

reactions, injection site reactions, and severe hypoglycemic events. There were no reports of hypersensitivity reactions in either treatment group, and no significant differences between groups for the incidence of injection site reactions (none in Process V and 1 report in Process VI) or severe hypoglycemic events (3 patients in Process V and 2 patients in Process VI).

Possible antibody neutralizing effect

The possibility of antibody neutralizing effect was assessed in patients who met the criteria for an increase of greater than 10% insulin cross-reactive AIA from baseline, AND ≥0.2% increase in HbA1c from baseline, AND an increase in their total insulin dose. At Week 12, 2 patients in Process V group and no patients in Process VI group met the criteria. At Week 18, 1 patient in Process V and 2 patients in Process VI met the criteria. No patient met the criteria at both Week 12 and Week 18, i.e., the effects of neutralizing antibody on HbA1c and insulin dose were not persistent. These results are consistent with low impact of antibody neutralizing effect in both the Process V and Process VI groups.

In conclusion, the OBP immunogenicity review during the first review cycle (original NDA submission) indicated no significant immunogenicity differences between Lantus and MYL-1501D produced using process V. The new data (Trial 3004) in the current submission demonstrate comparable immunogenicity for MYL-1501D produced via Process V and Process IV and provide further support for comparable immunogenicity between LANTUS and MYL-1501D. The Clinical Reviewer concurs with the OPB immunogenicity assessment.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hypoglycemia

The classification of hypoglycemic events used by the Applicant in this study is consistent with the classification used in prior clinical studies in the MYL-1501 Development Program, and is summarized below:

- Severe: requiring third party assistance to actively administer carbohydrate, glucagon, or other resuscitative actions which results in neurological recovery, regardless of the availability of a blood glucose measurement.
- Documented symptomatic: Event with typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration ≤70 mg/dL
- Asymptomatic: Event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL
- Probable symptomatic: Characteristic symptoms of hypoglycemia with no blood glucose levels measurement and that resolved with food intake, subcutaneous glucagon, or intravenous glucose

- Relative: Event in which the subject reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose >70 mg/dL
- Nocturnal hypoglycemia: Events that occurs from the time the subject goes to bed at night till the time the subject wakes up. This may include any of the above 5 types of hypoglycemia described. It is noted that the definition of nocturnal hypoglycemia in Table 26 of CSR is different and defined as an event occurring between 00:01h and 05:59 h, inclusive.

Hypoglycemic events and any associated symptoms were recorded only on the hypoglycemic episodes page of the CRF. Severe hypoglycemia and those episodes meeting any criteria of the ICH criteria for seriousness were recorded on both, the hypoglycemic episodes page and on the SAE and AE pages. Hypoglycemic episodes were analyzed separately from AEs.

The incidence of patients with at least one hypoglycemic event recorded by visit during the treatment period was similar between the Process V and Process VI groups in all categories of hypoglycemia reported. The incidence of patients with at least one hypoglycemic event at any visit is summarized by categories (selected the more clinically relevant categories) in Table 23.

Table 23: Incidence of patients with at least one hypoglycemic episode at any visit by selected categories

Category	MYL-1501D Process V (N=108) n (%)	MYL-1501D Process VI (N=110) n (%)	p-value
Any hypoglycemic event	105 (97.2)	105 (95.5)	0.7215
Severe hypoglycemia	3 (2.8)	4 (3.6)	1.0000
Documented symptomatic hypoglycemia	96 (88.9)	89 (80.9)	0.1003
Asymptomatic hypoglycemia	79 (73.1)	77 (70.0)	0.6064
Nocturnal hypoglycemia	82 (75.9)	80 (72.7)	0.5889

The incidence of hypoglycemic episodes during a time period on treatment was defined as the incidence of patients with at least one hypoglycemic episode occurring within that period of time. Nocturnal hypoglycemia was defined as episodes occurring between 00:01 h and 05:59 h, inclusive.
p-value from Chi-square test if 80% of the cell had an expected frequency ≥5, Fisher's exact test was used otherwise.
Source: excerpted from Table 14.3.3.3.1, CSR

The reported hypoglycemic event rates (expressed in number of episodes/30days) in the Process V group was similar to the rates in Process VI group (Process VI *minus* Process VI = 0.62, p=0.27). The mean actual rates at baseline were 6.25 episodes/30 days for Process V and 6.12 episodes/30 days for Process VI group. A significant decrease in rate relative to baseline was observed in both groups (-1.80 ± 4.97 for Process V and -1.68 ± 5.25) by Week 9 and maintained through Week 18 (-1.44 ± 4.81 for Process V and -0.85 ± 3.91 for Process VI). The similarity in incidence of hypoglycemic events between Process V and Process VI is also illustrated by the

actual hypoglycemic event rates (episodes/30 days) in Figure 9.

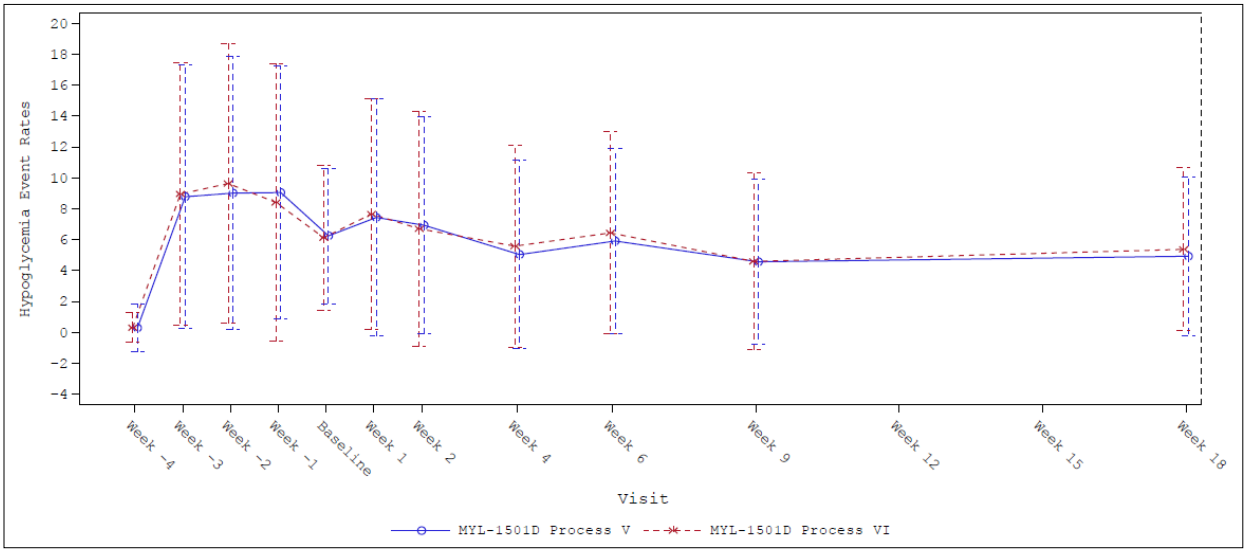

Figure 9: Actual hypoglycemic event rates (episodes/30 days) by visit and treatment (means and SD)
Blue line: Process V; red line: Process VI
Source: Excerpted from Figure 14.2.7.2, CSR

Two SAEs of severity grade 4 nocturnal hypoglycemia were assessed by the Investigator as possibly related to the IP. One patient was in the Process V group and the other was in Process VI group, and the blood glucose at the time of the event was 25 mg/dL and 24 mg/dL, respectively. Both experienced neuroglycopenic symptoms and reported having missed dinner the night prior to the hypoglycemic event. Only one patient had insulin dose reduced after the hypoglycemic episode. The narratives provided for these events do not contain enough information for further assessment of causality.

Severe hypoglycemia was reported by 3 patients in the Process V group and 4 patients in the Process VI group. All severe hypoglycemic events were characterized by neuroglycopenic symptoms, required third party assistance and improved after the patient received carbohydrates or glucagon (one patient in each group was treated with glucagon). No patients experienced seizures or any complications. The majority of the hypoglycemic events was related to the patient skipping an evening meal after injecting insulin.

8.6. Safety Analyses by Demographic Subgroups

The Applicant did not provide safety analyses by demographic subgroups, other than for cross-reactive insulin antibodies (see Section 8.4.10), which showed no statistically significant differences by gender, age or race.

8.7. Specific Safety Studies/Clinical Trials

Study MYL-1501D-3004 is a specific study that was conducted to address one of the issues included in the Complete Response Letter to the original NDA Application. The purpose of this study was to assess efficacy and safety similarity between the MYL-1501D product manufactured at the facility in India (Process V) and the MYL-1501D product manufactured at the facility in Malaysia (Process VI).

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No human carcinogenicity or tumor development studies were conducted within this clinical trial.

8.8.2. Human Reproduction and Pregnancy

No human reproduction and pregnancy studies were conducted within this clinical trial.

8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatrics and assessment of effects on growth were conducted within this clinical trial.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No assessments for overdose, drug abuse potential, withdrawal, and rebound were conducted in this study.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Since Study MYL-1501D-3004 has shown similarity in efficacy and safety between MYL-1501D Process VI product and MYL-1501D Process V product, the potential risks with the use of MYL-1501D Process VI are not expected to be different from those shown for Process V in previous clinical studies, i.e., hypoglycemia, hypersensitivity reactions and injection site reactions.

8.9.2. Expectations on Safety in the Postmarket Setting

The risks associated with MYL-1501D Process VI product remains the same as those originally associated with MYL-1501D Process V and insulin products in general, i.e., hypoglycemia, hypersensitivity reactions, and injection site reactions.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues from other disciplines were identified for MYL-1501D Process VI.

8.10. Integrated Assessment of Safety

The safety findings of the clinical trial MYL-1501D-3004 conducted to compare Process V and Process VI were consistent with the safety findings of the clinical trials submitted in the original NDA application and of the reference listed drug, Lantus. No new safety findings were identified.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting and other external consultations were conducted for this clinical trial.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant's proposed labeling for Semglee includes:

- changes consistent with Lantus labeling updates approved in November 29, 2018
- changes to incorporate the FDA recommendations in the Complete Response Letter dated May 17, 2018
- inclusion of summary data of the study MYL-1501D-3003 to support interchangeability

Reviewer's Comments: Our main labeling recommendations are listed below:

1. *The Applicant's proposed prescribing information (PI) was based on an outdated Lantus PI (November 2018). An updated (PLLR implemented) version of Lantus PI was approved in May 2019. However, rather than aligning Semglee's PI to Lantus' PI, we edited Semglee's label to harmonize with the most recently approved insulin labels.*
2. *Section 6.1 – Clinical Trial Experience: the values of baseline HbA1c were updated to be consistent with the Statistical Reviewer's findings for the studies submitted in the original application. In addition, Tables 1 to 4 were updated to show adverse reactions as opposed to adverse events in studies performed with Semglee and with another insulin glargine product.*
3. *Section 11 – Replace* [redacted] (b) (4) *for [the yeast Pichia pastoris] as the production organism used in the recombinant DNA technology for production of Semglee.*

4. *Section 12.2 – The pharmacodynamic (PD) data were updated by the Clinical Pharmacology Reviewer to reflect the PD profile for Process VI* (b) (4).
5. *In Section 14, the recommended changes include:*
    a. *Values in Table 9 and Table 12 were updated to reflect the findings of the Statistical Reviewer.*
    b. *Data in Tables 10, 11, 13 and 14 were updated to show only values related to HbA1c and Fasting blood glucose* (b) (4)

(b) (4)

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategies are recommended for this NDA.

12. Postmarketing Requirements and Commitments

No postmarketing requirements and commitments are recommended for this NDA.

13. Appendices

13.1. References

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2. Nathan, D.M., et al., *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group.* N Engl J Med, 1993. 329(14): p. 977-86.
3. Lachin, J.M., et al., *Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes, Interventions and Complications Research Group.* N Engl J Med, 2000. 342(6): p. 381-9.
4. Lachin, J.M., et al., *Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC.* Diabetes, 2015. 64(2): p. 631-42.
5. American Diabetes, A., *9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2019.* Diabetes Care, 2019. 42(Suppl 1): p. S90-S102.

13.2. Financial Disclosure

Please refer to the information on the original NDA review completed by Dr. Mitra Rauschecker on 04/30/2018. No new information was provided in the NDA resubmission package regarding financial disclosures.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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PATRICK ARCHDEACON
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CDTL Review and
Division Summary Memo for Regulatory Action

Date	May 17, 2018
From	Patrick Archdeacon, M.D.
Subject	Division of Metabolism and Endocrinology Products (DMEP) Summary Memo for Regulatory Action
NDA #	210605
Applicant	Mylan
Date of Submission Receipt	August 31, 2017; September 15, 2017 (file over protest)
PDUFA Goal Date	May 17, 2018
Proprietary Name / Established (USAN) names	Semglee Insulin glargine injection
Dosage forms / Strength	solution for sc injection 100 units/mL
Proposed Indication	Indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and adults with type 2 diabetes mellitus
Recommended Action	Complete Response

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Diabetes mellitus is a condition of impaired glucose metabolism that results in hyperglycemia. There are two types of diabetes: type 1 diabetes (T1DM) is distinguished by absolute insulin deficiency that is the result of autoimmune destruction of pancreatic beta cells; type 2 diabetes (T2DM) is characterized by either insulin resistance or a relative deficiency of insulin. Both types of diabetes increase the risk for microvascular and macrovascular complications. Insulin treatment is required for T1DM and is often necessary for patients with T2DM who are refractory to treatment with non-insulin antihyperglycemic agents.

The Applicant has submitted an NDA through the 505(b)(2) pathway for Semglee (MYL-1501D), a proposed insulin glargine product that relies, in part, on the FDA's finding of safety and effectiveness for US-approved Lantus (insulin glargine injection), the listed drug manufactured by Sanofi-Aventis. The NDA includes both a pen/cartridge presentation and vial presentation of MYL-1501D.

The NDA submission includes comparative analytical data, PK/PD euglycemic clamp studies, and two pivotal phase 3 trials (MYL-GAI-3001 conducted in a population of patients with T1DM and MYL-GAI-3002 conducted in a population of patients with T2DM). Of note, the MYL-1501D drug product used in the PK/PD clamp studies and pivotal phase 3 trials submitted to support the NDA was manufactured using a manufacturing process identified as "Process V". However, the Process V drug product is not the to-be-marketed product. In response to advice from the European Medicines Agency to reduce impurities in the drug substance, the Applicant changed to manufacturing MYL-1501D using a manufacturing process identified as "Process VI". The use of Process VI is intended to reduce (b) (4) of the drug substance and Process VI MYL-1501D is identified as the proposed to-be-marketed MYL-1501D drug product in the NDA submission. The applicant has not adequately bridged Process V and Process VI, which precludes a benefit-risk assessment of the proposed to-be-marketed drug product (i.e., MYL-1501D manufactured via Process VI). This deficiency was identified prior to NDA submission and was communicated to the applicant both prior to NDA submission and as part of a Refuse-to-File decision. The applicant requested that FDA file the NDA over protest.

Despite the identified deficiencies at the time of the NDA submission, FDA completed the review due to the Applicant's request that FDA file the NDA over protest. Review of the phase 3 trials supported a conclusion that Process V MYL-1501D was non-inferior to US-approved Lantus with regards to glycemic control as measured by change in HbA1c at 24 weeks. Similarly, review of the phase 3 trials supported a conclusion that the safety profile of Process V MYL-1501D was similar to US-approved Lantus. Review of the pivotal PK/PD clamp study supported a conclusion that the comparisons of Process VI MYL-1501D to Process V MYL-1501D and to US-approved Lantus met all of the pre-specified

primary PK and PD endpoints, though the comparison of Process V MYL-1501D to US-approved Lantus did not meet one of its pre-specified PD endpoints.

In addition to the clinical deficiencies known at the time of filing (e.g., the additional clinical safety and efficacy data needed to support a scientific bridge between Process VI MYL-1501D and Process V MYL-1501D based on the specific manufacturing changes made; the lack of PK/PD comparability data necessary to support the bridging between Process VI MYL-1501D in vials compared to Process VI MYL-1501D in cartridges), other deficiencies were identified during the review, including various product quality deficiencies (e.g., objectionable conditions observed at a manufacturing facility, deficient antimicrobial effectiveness testing (AET), lack of AET data supporting product expiry) and labeling deficiencies (including the prescribing information, the carton and container labeling, and the Instructions for Use).
As a result of the identified deficiencies, I am unable to conclude that there is a favorable Benefit-Risk assessment for the proposed to-be-marketed (i.e., Process VI) drug product.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diabetes mellitus is a serious chronic medical condition characterized by hyperglycemia and includes two main types: T1DM and T2DM • T1DM is caused by autoimmune destruction of the pancreatic beta cells, which leads to impaired insulin production and secretion, and impaired glucose metabolism. • T2DM is characterized by hyperglycemia either due to insulin resistance or a deficiency of insulin, and is often associated with other metabolic derangements, such as dyslipidemia, hypertension, and obesity. • Diabetes mellitus affects nearly thirty million people in the United States, the majority (90-95%) of these patients have T2DM, according to the Centers for Disease Control (CDC). • Acute life-threatening complications of T1DM include diabetic ketoacidosis due to insulin deficiency, while chronic complications of both T1DM and T2DM include cardiovascular disease, retinopathy, nephropathy, and neuropathy.	Both T1DM and T2DM are serious, life-threatening conditions that can lead to serious morbidity and mortality if left untreated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Due to the depletion of pancreatic beta cells which produce insulin, patients with T1DM require exogenous insulin for survival. Pramlintide, an amylin-mimetic, is also approved as adjunctive therapy to insulin. • Treatment options for T2DM includes lifestyle modifications, usually followed by the addition of one or multiple different medications[7]. There are currently multiple classes of pharmacologic treatments for T2DM, with multiple members of each class, including biguanides, sulfonylureas, insulin and insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose linked transporter (SGLT)-2 inhibitors.	Intensive insulin therapy is the standard of care for patients with T1DM. Patients with T2DM often require multiple agents for glycemic control, and due to the progressive nature of the disease, may also require insulin to achieve glycemic targets.
Benefit	• The Applicant is relying, in part, on FDA's finding of safety and effectiveness for the listed drug Lantus. Comparative clinical data from Trial 3001 (T1DM subjects) and Trial 3002 (T2DM subjects) demonstrated that MYL-1501D in combination with other antihyperglycemic agents (prandial insulin in Trial 3001 and oral antihyperglycemic agents in Trial 3002) was non-inferior to Lantus in change in HbA1c from baseline to Week 24.	The Phase 3 clinical trials for MYL IG generated by Process V support the conclusion that MYL IG is non-inferior to Lantus in patients with T1DM and T2DM and support the reliance on FDA's finding of safety and effectiveness for the listed drug, Lantus.
Risk and Risk Management	• The risks identified for MYL-1501D during the Phase 3 studies were similar to the previously identified risks associated with Lantus use. No new safety signals were identified for the MYL IG produced by Process V. Additional clinical safety and efficacy data are needed to support a scientific bridge between Process VI MYL-1501D and Process V MYL-1501D based on the specific manufacturing changes made.	The risks associated with the Process VI product are unknown. Additional clinical safety and efficacy bridging data are required to determine whether the data generated using Process V are relevant to the Process VI product.

2. Introduction

This document contains the 'Summary Basis for Regulatory Action' memo for NDA 210605 for MYL-1501D [proposed proprietary name: Semglee]; insulin glargine disposable pen presentation and vial presentation). The NDA was submitted through the 505(b)(2) regulatory pathway and relies, in part, on FDA's finding of safety and effectiveness for Lantus (NDA 21081; insulin glargine injection), approved on April 20, 2000. Lantus is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. NDA 210605 describes the use of Semglee in combination with the (b) (4) disposable pen; this presentation of Semglee is therefore a combination product. NDA 210605 also includes a presentation of Semglee in a 10 mL vial.

The reader is referred to the individual discipline reviews for a more comprehensive review and detailed discussion of the MYL-1501D development program.

This memo references the following documents/sources:

Subject	Author	Date
Clinical Efficacy and Safety Review (DMEP)	Dr. Mitra Rauschecker	April 30, 2018
Clinical Pharmacology (OCP) review	Dr. Jing Niu	April 24, 2018
Nonclinical Pharmacology Toxicology review (DMEP)	Dr. Arulasanam Thilagar	April 10, 2018
OPQ review	Multiple contributors (17 total)	April 5, 2018
DMEPA labeling review	Dr. Ariane Conrad	April 4, 2018
Immunogenicity review	Dr. Frederick Mills	April 25, 2018
CDRH consult review	Dr. Rong Guo	March 27, 2018
OSI review	Dr. Kleppinger	March 14, 2018
Statistics	Dr. Ketterman	April 16, 2018
OSIS review	Dr. Mahadevan	March 22, 2018
***Product quality includes reviews from ONDP (drug substance, drug product) and OPF (process, facility, and microbiology)** **DMEPA: Division of Medication Error and Prevention; CDRH: Center for Devices and Radiologic Health; OSIS: Office of Study Integrity and Surveillance; OSI: Office of Scientific Investigations**		

3. Background

Insulin glargine is a recombinant, long-acting, human insulin analog. Insulin glargine is administered subcutaneously and exerts a glucose lowering effect that lasts for up to 24 hours. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginine residues are added to the C-terminus of the B-chain. These structural modifications shift the molecule's isoelectric point (b) (4), rendering it soluble at pH 4 (clear solution in the vial) (b) (4) (b) (4) (b) (4)

The listed drug, US-approved Lantus, is an insulin glargine product approved in April 2000. Lantus is currently marketed in the US and other countries.

Regulatory History

IND 105279, under which MYL-1501D was developed, was originally opened by Biocon SA. Sponsorship of the IND was transferred from Biocon to Mylan in August of 2013. During the End-of-Phase 2 meeting to discuss the Phase 3 clinical program, the Applicant discussed its intent to transfer manufacturing of the drug substance from the manufacturing site in India to a manufacturing site in Malaysia. In addition to a geographic change, the Applicant also proposed changes to the manufacturing process of the drug substance (from Process V to Process VI). The manufacturing process changes were introduced in response to recommendations from EMA, in order to reduce impurities present in the Process V DS. At the End-of-Phase 2 meeting, FDA advised that additional nonclinical and/or clinical studies may be required if FDA determined that the change in manufacturing process resulted in any differences in quality attributes.

The Phase 3 pivotal trials supporting the current NDA were conducted with MYL-1501D produced by Process V. However, the Applicant is requesting approval of MYL-1501D produced by Process VI. In February 2016, FDA provided Type C written responses providing advice about plans to develop a bridge from MYL-1501D produced by Process V (hereafter referred to as Process V MYL-1501D) to MYL-1501D produced by Process VI (hereafter referred to as Process VI MYL-1501D). In those responses, FDA advised the Applicant that FDA did not agree with the proposal to submit the NDA for Process VI MYL-1501D relying only on analytical comparability data to bridge to Process V. In April 2016, FDA responded to the Applicant's request for clarification of its position: FDA reiterated that preliminary data showed that Process VI reduces (b) (4) of the drug substance, among other potential differences in quality attributes of the drug substance. For that reason, FDA believed that the change in processes could have a potential impact on the efficacy, safety, and immunogenicity of the MYL-1501D drug product. FDA did not agree with the Applicant's proposal to submit the NDA for the Process VI drug product with only analytical comparability data providing a bridge to the data generated with the Process V drug product; instead, FDA recommended that the Applicant submit its NDA for the Process V drug product. In November 2016, FDA recommended that a PK/PD study should be conducted to compare the Process VI drug product with the Product V drug product and with US-approved Lantus. Additionally, FDA informed the Applicant that an immunogenicity risk assessment would

need to be completed by FDA's Office of Biotechnology Products (OBP). On April 27, 2017, prior to the completion of the immunogenicity risk assessment, the Applicant submitted NDA 210605 requesting approval of the Process VI drug product.

On June 26, 2017, FDA notified the Applicant that it had determined that its application was not sufficiently complete to permit a substantive review and had therefore been classified as Refuse to File. Based on the specific manufacturing changes made, FDA stated that additional clinical safety and efficacy data (including an immunogenicity assessment) were needed to establish that the safety and efficacy data generated with Process V MYL-1501D are relevant to Process VI MYL-1501D and can be used to support a determination that the proposed to-be-marketed product is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus. In addition, the Agency described concerns regarding the results of a PK/PD study (MYL-1501D-1001) conducted to show PK/PD similarity between Process V and Lantus.

On August 15, 2017, a Type A meeting was held to discuss the Refuse to File decision. At that meeting, the Applicant was informed that they could request that the application be Filed Over Protest and that the Agency would be obliged to review the application. At that meeting, the Applicant was also advised to conduct an 18-week clinical study to support a bridge between the Process V and Process VI drug products. On August 31, 2017, the Applicant requested that its NDA be Filed over Protest. On September 19, 2017, the Applicant submitted a clinical protocol to IND 105279 for an 18-week clinical bridging study.

4. CMC/Device

The Office of Pharmaceutical Quality (OPQ) performed the overall quality/CMC review. The overall recommendation from OPQ for NDA 210605 was against approval due to identified issues with the manufacturing facility and the microbiological control of the products. I concur with the recommendations from OPQ, including the deficiencies cited as well as their recommendations to address these issues.

Specifically, OPQ cited objectionable conditions at the commercial manufacturing facility that require corrective actions (b) (4) (b) (4). The CMC microbiology review noted a lack of method suitability data for endotoxin, sterility, and antimicrobial effectiveness testing (AET) and a lack of AET data supporting the product expiry from stability. The microbiology deficiencies require the Applicant to provide AET results for the 10 mL vial drug product presentation (b) (4) at or below the minimum specification for release or stability testing (whichever is lower); to conduct antimicrobial effectiveness testing per USP<51> or equivalent methodology on at least one primary stability batch corresponding to 3 mL cartridge and 10 mL vial presentation at the end of shelf life and provide AET results to support the acceptability of the product at the end of expiry; and to provide study reports showing actual results to support the suitability of endotoxin and sterility methods used for analyzing 10 mL vial and 3 ml cartridge presentations.

Drug Substance

Dr. Joseph Leginus reviewed the CMC information provided for MYL-1501D drug substance (DS) and concluded that the DS information provided is adequate to support the NDA application for Process VI MYL-1501D. However, Dr. Leginus also found that a conclusion on analytical comparability of the Process V DS and Process VI DS cannot be made due to the significant difference in levels of impurities between the two drug substances. I concur with his conclusions.

The MYL-1501D drug substance is recombinant insulin glargine. Insulin glargine belongs to the established pharmacologic class of long-acting human insulin analogs. The proposed MYL-1501D drug product and the listed drug are clear, colorless solutions filled in 10 ml vial or in 3 ml prefilled pens and are intended for subcutaneous injection. Both products have the same composition and strength.

The Applicant provided an analytical similarity comparison between MYL-1501D injection and Lantus using multiple batches of each product in vial and prefilled pen (PFP) presentations. Due to differences in the manufacturing processes (Yeast strain for MYL-1501D and *E coli* strain for Lantus), subtle differences are expected in their product/process related impurity profiles. It is not feasible to compare the levels of impurities such as host cell proteins, single chain precursor, or glycosylated variants between MYL-1501D and Lantus, but impurity profile comparison between the two products are valid for common impurities arising from degradation of insulin glargine during manufacturing and storage. The analytical similarity exercise indicated sufficiently similar quality characteristics with respect to primary, secondary, tertiary, and higher order structure of insulin glargine, as well as biological activity and IGF-1 receptor binding affinity.

MYL-1501D is manufactured from an insulin glargine precursor expressed in *Pichia pastoris* expression system. (b) (4)

(b) (4)

During development, the manufacturing operation of both the DS and the drug product (DP) were moved from Biocon Ltd.., Bangalore, India to Biocon Sdn. Bhd., Malaysia. During this move, the Applicant scaled up the fermentation process from (b) (4) (Process V) to (b) (4) (Process VI) and implemented changes to chromatographic purification conditions. The changes improved the purity of the Process VI DS without introducing new impurities; compared to the Process V DS, the Process VI DS has fewer (b) (4) and lower levels of total impurities. Dr. Leginus notes that as a result a conclusion on analytical comparability of the Process V DS and Process VI DS cannot be made due to the significant difference in levels of impurities between the two drug substances.

The analysis of the Process VI DS included confirming the primary structure by amino acid sequencing, mass spectroscopy, and peptide mapping. Higher order structure was analyzed by

X-ray structure, UV-Vis, near UV and Far UV CD, FT-IR, and NMR spectra in comparison with DS extracted from Lantus. Biological activity of DS was demonstrated by total insulin receptor phosphorylation and IGF-1 receptor binding affinity assays as well as by in vivo bioassay. The proposed specifications for insulin glargine conform to USP Insulin glargine monograph.

CDTL comment: Dr Leginus concluded in the DS review that the drug substance information is adequate to support the approval of the NDA submitted in support of the Process VI DS. His determination that a conclusion on the analytical comparability between Process V and Process VI cannot be made, however, has the consequence of requiring additional data to bridge from Process V MYL-1501D to Process VI MYL-1501D in order for the NDA submitted for approval of Process VI MYL-1501D to rely on the clinical trial data generated using Process V MYL-1501D. I concur with his conclusion. The Applicant was advised in June of 2017 that FDA had determined that its application was not sufficiently complete to permit a substantive review and had therefore been classified as Refuse to File. The analytical comparability data and concerns regarding the results of the PK/PD study (MYL-1501D-1001) were cited (see Section 6 for details regarding the PK/PD study). On August 15, 2017, a Type A meeting was held to discuss the Refuse to File determination. At that August 15, 2017 Refuse-to-File meeting, the Applicant was advised to conduct an 18-week clinical study to support a bridge between the Process V and Process VI drug products.

Drug Product

Dr. Joanne Wang reviewed the batch formula, manufacturing process description, process development, and process validation information and concluded that the NDA contains adequate description of the process used for manufacturing MYL-1501D vials and prefilled pens. I concur with her conclusion.

MYL-1501D 100 U/mL is a sterile, aqueous, clear, colorless solution filled in 10mL vial or as 3mL prefilled pen (PFP). The proposed final formulation is the same as that used in development and Phase 3 clinical studies. The drug product (DP) contains 3.64 mg insulin glargine, glycerol (20 mg), metacresol (2.7 mg), zinc chloride (30 mcg), and water for injection USP. The vial product, but not the PFP, also contains 20 µg/mL of Polysorbate 20 (b) (4).

CDTL comment: The vial presentation and pen/cartridge presentation of MYL-1501D use different formulations of MYL-1501D, but the phase 3 trials evaluated only the pen/cartridge presentation. For that reason, data demonstrating PK/PD comparability of the two is necessary to bridge the two formulations in order to make conclusions about the vial presentation of MYL-1501D. A recommendation to conduct a PK/PD comparability study between the cartridge and vial presentations was conveyed to the Applicant during the August 15, 2017 type A Refuse-to-File meeting.

Primary container closure system

The drug product filled in USP Type 1 glass cartridge (3mL) contains a (b) (4) rubber disc on one end and a (b) (4) rubber plunger on the other end. The drug product filled in 10 mL vial contains a rubber stopper as closure. The closure system components are known for use in parenteral products or the same as in approved insulin products and are acceptable for proposed use.

Microbiology

Dr. Jennifer Patro reviewed the microbiological controls associated with the drug product manufacturing process, (b) (4) (b) (4) validation, environmental monitoring, container closure integrity, antimicrobial effectiveness testing, sterility and endotoxin testing (drug product specification), stability data, and post-approval stability commitment. Dr. Patro identified the following deficiencies: 1) the Applicant did not provide product specific method verification information for sterility, endotoxin, and preservative efficacy; 2) the Applicant did not conduct antimicrobial testing on product during stability at the end of expiry. I concur with her conclusions.

Immunogenicity

Dr. Frederick Mills reviewed the assay for detection of anti-drug antibodies (ADA) to MYL-1501. The assay was also used to detect ADA to the comparator product, Lantus, as well as antibodies that react with insulin. His review also evaluated a yeast host-cell protein (HCP) antibody-based assay. Dr. Mills concluded, and I concur, that both antibody assays are adequately validated. Dr. Mills notes that the assays were used to evaluate immunogenicity in clinical studies that used drug substance produced by Process V, but that the assays should be adequate to evaluate immunogenicity in trials using drug substance produced by Process VI.

Dr. Mills reviewed the immunogenicity profiles from the patient antibody data generated in the pivotal clinical trials using the Process V DS. Overall, he concluded that the immunogenicity profiles were similar between the MYL-1501D and US-approved Lantus treatment groups. He also found that the proportions of patients who tested positive for anti-HCP antibodies were comparable between treatment groups.

Dr. Mills also reviewed an immunogenicity assessment submitted by the Applicant related to the potential risks resulting from the Process V to Process VI change. Dr. Mills notes that the factors most likely to impact immunogenicity (amino acid sequence, impurities, aggregation, and stability) suggest no increased immunogenicity due to exposure to the Process VI DS compared to the Process V DS.

His review also comments on two protocols submitted to IND 105279: MYL-1501-1003 (a clamp study to compare the PK/PD of MYL-1501D Process V and MYL-1501D Process VI with US Lantus) and MYL-1501-3004 (a clinical study comparing the efficacy and safety of MYL-1501D Process V and MYL-1501D Process VI). Dr. Mills states that the sampling plan

"provides adequate coverage to assess the time course of the immunogenicity response extending from baseline, through early responses, mid-course, and long-term ADA development. Therefore, overall the protocol should be adequate to assess immunogenicity comparability between process V and VI for MYL-1501D."

CDTL comment: I concur with Dr. Mill's assessment of the performance of the assays and the findings regarding the immunogenicity profiles generated in the pivotal clinical trials using the Process V DS. While Dr. Mills suggests it is unlikely that Process VI DS would be more immunogenic than Process V DS, his review suggests that the Process V DS could be more immunogenic that the Process VI DS (due to the higher amounts of impurities associated with Process V). Given that the clinical significance of anti-insulin antibodiesare poorly understood, it is possible that a less immunogenic insulin glargine (e.g., Process VI MYL-1501D) could exhibit clinically important differences from a more immunogenic insulin glargine (Process V MYL-1501D).

Center for Devices and Radiological Health (CDRH)

Dr. Rong Guo recommends approval of the device constituent of the combination product. I concur with the recommendation of Dr Guo. The scope of Dr. Guo's review included the submission materials intended to support the safety and functionality of the pre-filled pen injector (dose accuracy, functional performance, biocompatibility of non-primary closure components), but not the manufacturing of the pen injector nor the human factors study.

As previously noted, one presentation of Semglee in NDA 210605 is as a disposable pre-filled pen (PFP). The (b) (4) Disposable pen is intended to deliver a maximum of 80 insulin glargine units (U) per injection and the total deliverable content of the MYL-1501D cartridge is 300 U; the combination product of the (b) (4) Disposable pen and the MYL-1501D cartridge will be referred to as the MYL-1501D PFP in this review. The MYL-1501D PFP contains 3 mL of 100 U/mL insulin glargine. Doses are set from 1 to 80 U in increments of 1 U.

Dose accuracy and functional performance was tested in accordance with ISO 11608:1-2014. Dr. Guo found that the dose accuracy performance met the ISO acceptance criteria and therefore demonstrated the acceptable delivery performance of the commercial pen configuration of ML-1501D PFP. Dr. Guo also determined that four difference commercial needles tested passed the requirement for general fit and attachment and removal torque. Dr. Guo also found that the biocompatibility information provided is appropriate and acceptable for the intended use.

Facility Compliance

Dr. Vidya Pai reviewed the facility compliance information for drug product and drug substance manufacturing facilities. The FDA's pre-approval inspection of the drug substance and drug product manufacturing facility between Feb. 6th and Feb. 15th resulted in a withhold recommendation due to objectionable conditions observed at the commercial manufacturing facility. To correct these deficiencies, the Applicant has committed to completing several

corrective actions (b) (4) (b) (4). Implementation of corrective actions is required before the facility can be considered as acceptable to support the NDA. I concur with the conclusions of Dr. Pai.

5. Nonclinical Pharmacology/Toxicology

Dr. Arulasanam Thilagar reviewed the nonclinical data submitted to the NDA. He found that the pharmacology/toxicology data supports a determination that NDA is approvable; I concur with his recommendation.

The Applicant conducted in vitro pharmacology assays, in vivo pharmacodynamic (PD) and pharmacokinetic (PK) studies, along with in vitro insulin receptor (IR), insulin-like growth factor-1 receptor (IGF-IR) binding studies, cell-based receptor-dependent metabolism and mitogenicity studies, and a repeat-dose rat toxicity study to compare MYL-1501D and US-approved Lantus. The Applicant conducted many nonclinical studies with Process V MYL-1501 D drug substance in addition to the head-to-head nonclinical in vitro and in vivo studies with Process VI MYL-1501D and US-approved Lantus that were found by Dr. Thilagar to provide adequate support to the NDA submission. The review of the submitted studies evaluated all the in vitro and in vivo toxicology studies comparing Process VI MYL-1501D and US-approved Lantus. Dr Thilagar found that those pharmacology/toxicology data support the similarity of Process VI MYL-1501D and US-approved Lantus. Dr. Thilagar did not review all of the nonclinical studies that used formulations different from the Process VI MYL-1501D formulation or performed with comparators other than US-approved Lantus. Please see his review in DARRTS dated April 10, 2018 for details.

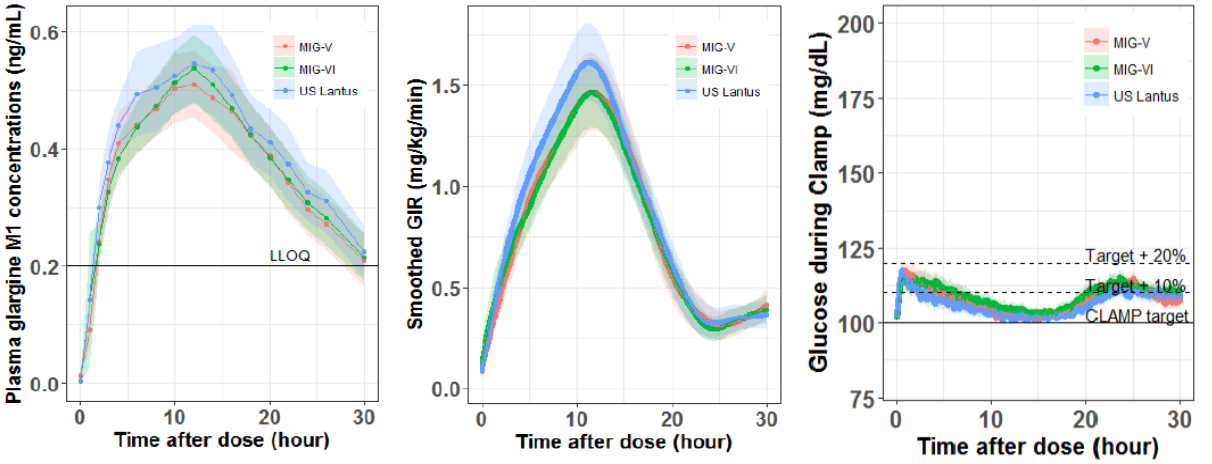
6. Clinical Pharmacology/Biopharmaceutics

Dr. Jing Niu evaluated the clinical pharmacology data and found them acceptable to support the approval of NDA 210605, pending the resolution of clinical concerns arising from the manufacturing process change from Process V MYL-1501D to Process VI MYL-1501D. Please see the Clinical Pharmacology review submitted on April 24, 2018 for details.

The clinical pharmacology review evaluated data from two euglycemic clamp studies. Study MYL-1501D-1001 compared the PK and PD profiles of Process V MYL-1501D, Process VI MYL-1501D, and US-approved Lantus after a single subcutaneous dose of 0.5 unit/kg; study GLARGCT100111 compared the PK and PD profiles of Process V MYL-1501D, US-approved Lantus, and EU-approved Lantus after a single subcutaneous dose of 0.4 unit/kg. The clinical pharmacology review also considered the data from the two phase 3 studies (MYL-GAI-3001 and MYL-GAI-3002) to inform its conclusions based of the evaluation of the clinical pharmacology studies. The results of MYL-GAI-3001 and MYL-GAI-3002 are also discussed in Section 7 (Clinical/Statistical Efficacy).

Dr. Niu concluded from the evaluation of study MYL-1501D-1001 that the comparison of Process VI MYL-1501D to Process V MYL-1501D and to US-approved Lantus met the prespecified criteria (geometric mean ratios and 90% CI within 0.8 – 1.25) for the primary PK (C_{max} and $AUC_{0\text{-}24h}$) and PD (GIR_{max} and $AUC_{GIR0\text{-}24h}$) parameters. For the comparison of Process V MYL-1501D to US-approved Lantus, the prespecified "goalposts" were met for C_{max}, $AUC_{0\text{-}24h}$, and GIR_{max} but not for $AUC_{GIR0\text{-}24h}$. For the comparison of Process V MYL-1501D to US-approved Lantus, the 90% CI was (0.783; 0.985). Dr Niu concluded that the data from MYL-1501D-1001 demonstrated PK/PD similarity between Process VI MYL-1501D and US-approved Lantus. Dr. Niu also concluded that the data from MYL-1501D-1001 demonstrated PK/PD similarity between Process VI MYL-1501D and Process V MYL-1501D. While the PD data for $AUC_{GIR0\text{-}24h}$ did not meet the prespecified criterion for the lower limit of the confidence interval, Dr Niu concluded (and I agree) that the totality of the evidence including the safety and efficacy data from the Phase 3 clinical trials which compared Process V MYL-1501D to US-approved Lantus support the conclusion that any differences between Process V MYL-1501D and US-approved Lantus are not clinically relevant.

Figure 1: Mean (90% ci) insulin glargine concentration - time; smoothed GIR -time; blood glucose concentration - time plots (Study MYL-1501D-1001)



(Source: Clinical Pharmacology Review)

Table 1: Statistical analysis of primary PK and PD parameters in MYL-1501D-1001

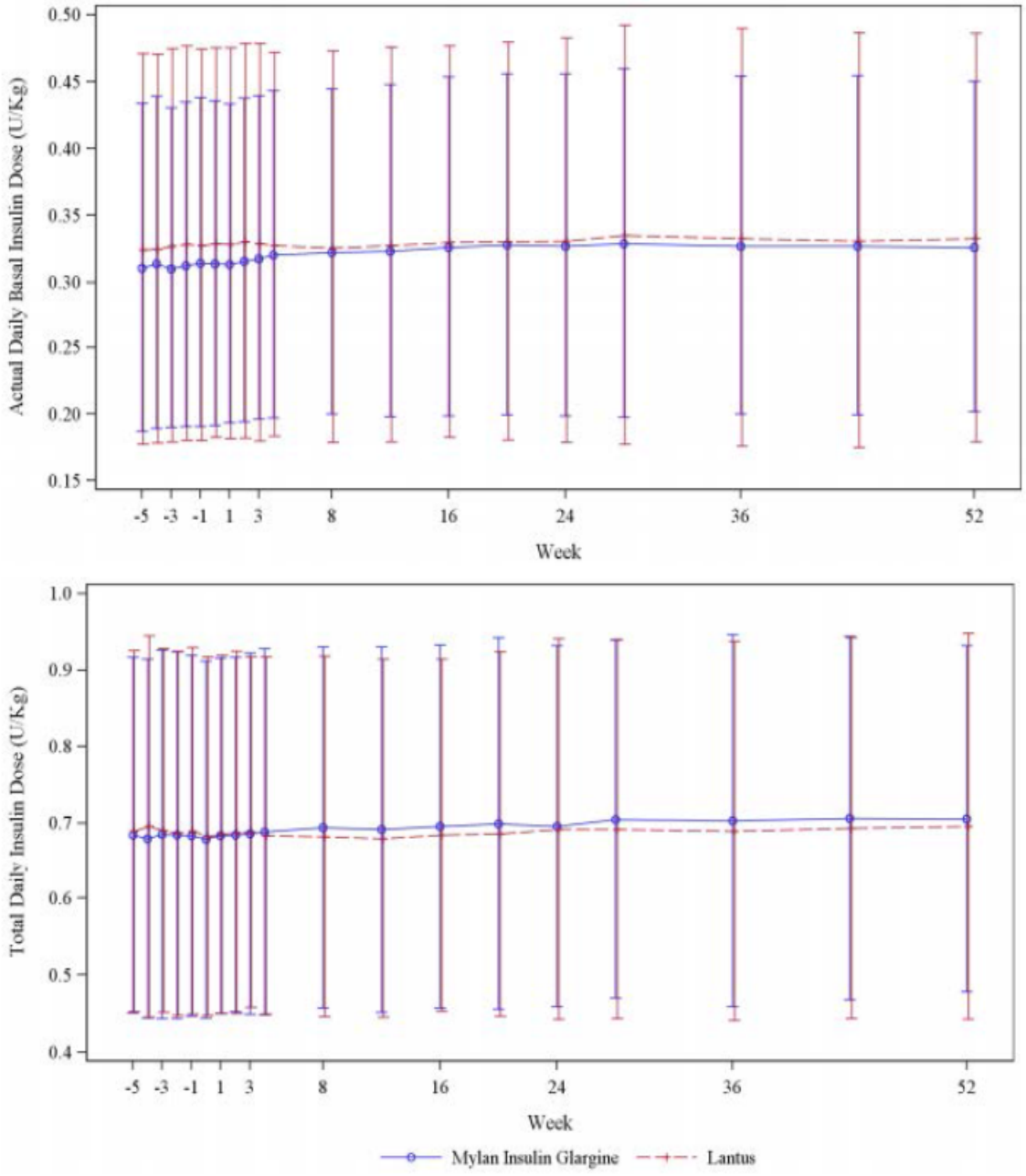
Type	Parameter	Geometric Mean Ratio (%)	90% CI
MIG-VI vs. US-Lantus			
PK	C_{max}	100.60	(94.95; 106.58)
	AUC_{0-24h}	96.75	(91.49; 102.31)
PD	GIR_{max}	93.79	(84.59; 103.98)
	$AUC_{GIR0-24h}$	92.35	(80.25; 106.27)
MIG-VI vs. MIG-V			
PK	C_{max}	108.03	(101.69; 114.77)
	AUC_{0-24h}	105.08	(99.14; 111.37)
PD	GIR_{max}	102.87	(94.05; 112.51)
	$AUC_{GIR0-24h}$	108.21	(95.58; 122.52)
MIG-V vs. US-Lantus			
PK	C_{max}	94.18	(89.55; 99.06)
	AUC_{0-24h}	92.82	(88.30; 97.56)
PD	GIR_{max}	93.07	(85.55; 101.24)
	$AUC_{GIR0-24h}$	87.81	(78.30; 98.47)

Source: Sponsor's analysis

CDTL comment: While MYL-1501D-1001 provides important data supporting a conclusion of PK/PD comparability between Process VI MYL-1501D and Process V MYL-1501D, the results of the PK/PD study are not sufficient to bridge between Process VI MYL-1501D and Process V MYL-1501D such that this NDA submitted for Process VI MYL-1501D can rely on clinical trials conducted with Process V MYL-1501D to support safety and efficacy for the following reasons: 1) the topline results of MYL-1501D-1001 are not entirely reassuring, as not all of the primary endpoints were met for each of the three-way comparisons, 2) the PK/PD study does not provide adequate data to inform whether any differences in the immunogenicity of Process VI MYL-1501D and Process V MYL-1501D could directly or indirectly affect efficacy or safety. As communicated to the Applicant in the Refuse to File letter, based on the specific manufacturing changes made, additional clinical safety and efficacy bridging data, including an assessment of immunogenicity, are needed to establish that the efficacy and safety data generated with Process VI MYL-1501D are relevant to the Process VI product. As explained at the August 15, 2017, Informal Conference to discuss the Refuse to File decision, the clinical study "should evaluate the potential impact of differences in immunogenicity between the Process V and Process VI products on clinical parameters such as insulin dose requirement, glycemic control, local tolerability, hypersensitivity reactions, and hypoglycemia risk in the intended use setting."

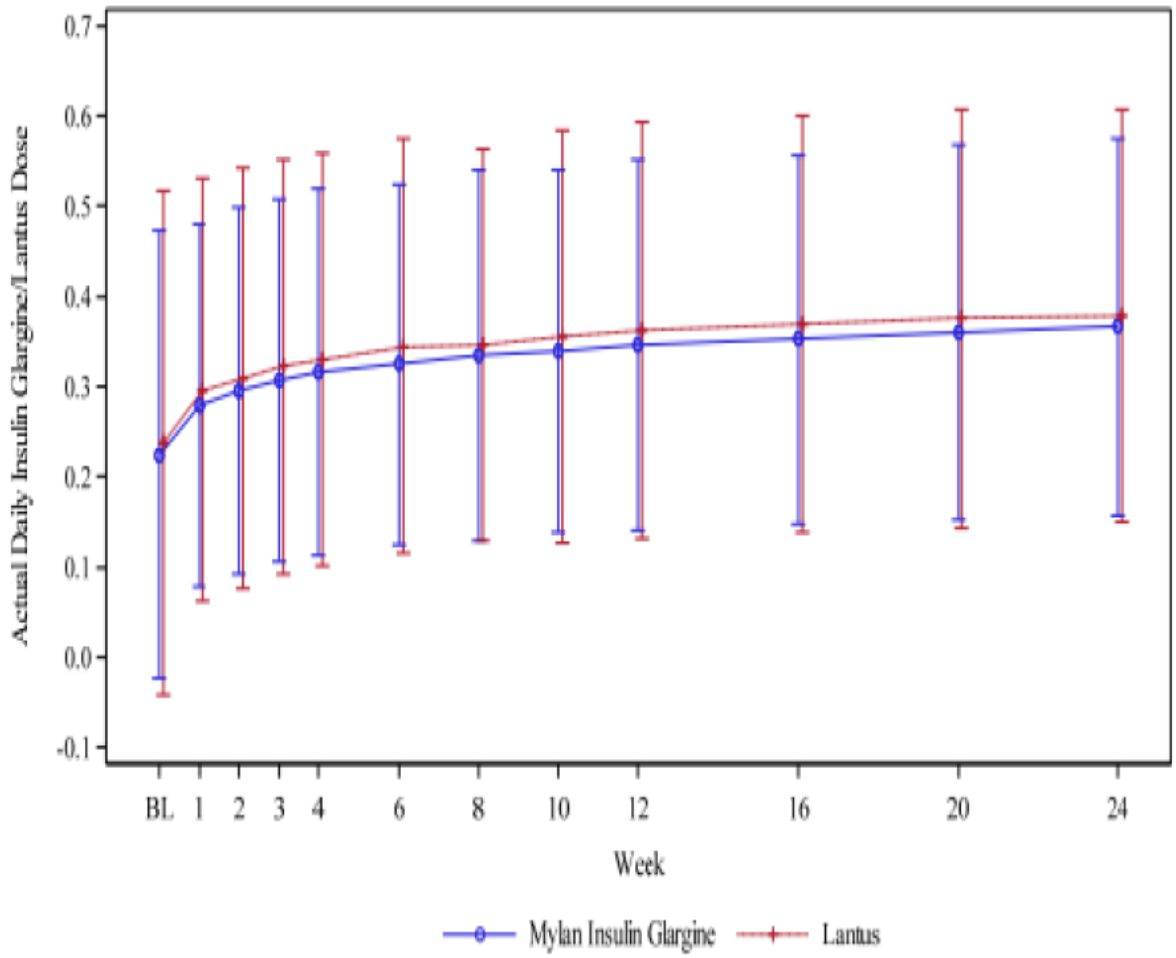
Dr. Niu evaluated the PK data from MYL-GAI-3001 and MYL-GAI-3002. Based on the observed overall dose-time profiles for the basal and total insulin used in these studies, Dr. Niu concluded that dose utilization of MYL-1501D and US-approved Lantus were not different in these trials.

Figure 2: Overall daily mean basal and total insulin dose by treatment in MYL-GAI-3001



Source: CSR of study MYL-GAI-3001– Figure 11-6 and Figure 11-7

Figure 3: Overall daily mean basal insulin by treatment in MYL-GAI-3002



Source: CSR of study MYL-GAI-3002– Figure 11-5

Dr. Niu concluded that that data from GLARGCT100111 provided additional support for the conclusions based on MYL-1501D-1001, MYL-GAI-3001, and MYL-GAI-3002. Because GLARGCT100111 did not study the proposed to-be-marketed product (Process VI MYL-1501D), the study was considered supportive only. For that reason, Dr. Niu relied on the analyses of the Applicant and did not conduct separate FDA analyses. In GLARGCT100111, the comparisons of Process V MYL-1501D to US-approved Lantus met the prespecified criteria for the primary PK ($C_{ins,max}$ and $AUC_{ins.0-30h}$) and PD (GIR_{max} and $AUC_{GIR0-30h}$).

CDTL comment: The conclusion of PK/PD similarity between Process V MYL-1501D and US-approved Lantus in GLARGCT100111 is consistent with the conclusion that the differences observed between Process V MYL-1501D and US-approved Lantus in MYL-1501D-1001 are not clinically relevant.

Dr. Niu noted that only the formulation from the cartridge presentation of MYL-1501D was studied in MYL-1501D-1001, MYL-GAI-3001, and MYL-GAI-3002. The vial formulation includes [redacted] (b) (4) (polysorbate-20). For that reason, Dr. Niu identified the

lack of data demonstrating PK/PD comparability of the two formulations as a deficiency in the NDA submission. Dr. Niu further noted that a recommendation to conduct a PK/PD comparability study between the cartridge and vial presentations was conveyed to the Applicant during the August 15, 2017 type A Refuse-to-File meeting. Subsequent to that meeting, the Applicant submitted a protocol of a two-way PK/PD study to investigate the bioequivalence of Process VI MYL-1501D in vials compared to Process VI MYL-1501D in cartridges (Study MYL1501D-1004).

CDTL comment: The lack of data demonstrating PK/PD comparability of the vial presentation to the cartridge presentation of Process VI MYL-1501D will be included as a deficiency in the Complete Response Letter.

7. Clinical/Statistical- Efficacy

Dr. Anna Ketterman and Dr. Mitra Rauschecker evaluated the clinical trial data submitted to the NDA to demonstrate the efficacy of MYL-1501D. Both Dr. Ketterman and Dr. Rauschecker concluded, and I concur, that the submitted data demonstrate the non-inferiority of Process V MYL-1501D to US-approved Lantus. However, additional clinical safety and efficacy bridging data between Process VI MYL-1501D and Process V MYL-1501D are needed to establish the relevance of data generated with Process V MYL-1501D to support a determination that Process VI MYL-1501D is non-inferior to US-approved Lantus. Dr. Ketterman recommends, and I concur, that any efficacy results based on these submitted data that are included in any future labeling should reflect the FDA analyses that used the return to baseline imputation approach and not the Applicant's analyses that used the mixed effects with repeated measures (MMRM) model.

The pivotal Phase 3 trials to establish efficacy were MYL-GAI-3001 (in a population of patients with T1DM) and MYL-GAI-3002 (in a population of patients with T2DM). Additional studies in patients with T1DM were conducted using populations of Japanese and Indian patients, but the data for those studies were not submitted to the NDA. Both studies relied on a non-inferiority design, using US-approved Lantus as the active comparator. MYL-GAI-3001 and MYL-GAI-3002 both evaluated Process V MYL-1501D in the cartridge formulation only. Both studies were designed to demonstrate the non-inferiority of MYL-1501D to US-approved Lantus for the endpoint of change in HbA1c after 24 weeks of treatment with a margin of 0.4%. Of note, both studies used an open label design.

CDTL comment: As previously discussed, because the pivotal Phase 3 studies evaluated the Process V MYL-1501D product, a scientific bridge from Process V MYL-1501D to Process VI MYL-1501D is needed to rely on these studies to support a determination that the Process VI product is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus and to demonstrate the efficacy of the Process VI MYL-1501D product. Also, as previously discussed, because the formulation of the vial presentation differs from the cartridge formulation and because the pivotal Phase 3 studies evaluated only the pre-filled pen/cartridge presentation, data establishing the bioequivalence of Process VI MYL-1501D in vials compared to Process VI MYL-1501D in cartridges are necessary to support the

efficacy of the vial presentation of MYL-1501D. The analyses discussed in the rest of this section pertain to the evidence supporting the efficacy of the pre-filled pen/cartridge presentation of Process V MYL-1501D.

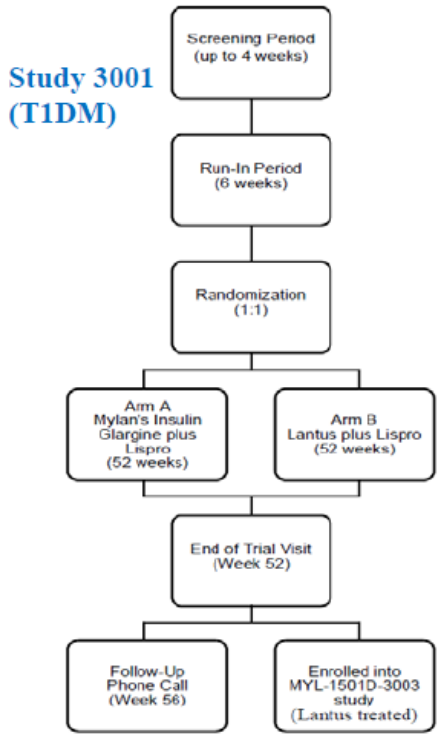
Table 2: Pivotal Phase 3 Studies to Demonstrate the Efficacy of Process V MYL-1501D

Phase 3 Studies to Support Efficacy and Safety						
NCT02227862/ MYL-GAI-3001	Efficacy and safety: randomized, open-label, multicenter, parallel group trial	MYL IG SC pre-filled pen vs. Lantus-US SC pre-filled pen	1°: NI in change from BL to 24 weeks in HbA1c	T1DM subjects	Run-in: 6 weeks Randomized period: 52 weeks	558 randomized, 517 completed
NCT02227875/ MYL-GAI-3002	Efficacy and safety: randomized, open-label, multicenter, parallel group trial	MYL IG SC pre-filled pen vs. Lantus-US SC pre-filled pen	1°: NI in change from BL to 24 weeks in HbA1c	T2DM subjects	Randomized period: 24 weeks	560 randomized, 490 completed

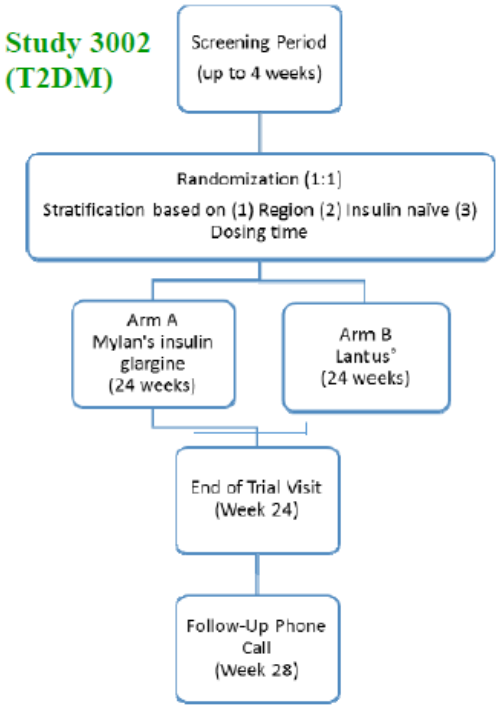
Abbreviations: IU, International units; NI, non-inferiority; BL, baseline; SC, subcutaneous; Lantus-US, Lantus approved in the United States; Lantus-EU, Lantus approved in the European Union

Source: FDA Clinical Review

Figure 4: Study Design for Pivotal Phase 3 Studies of MYL-1501D



Source: CSR P.36



Source: CSR p. 30

The primary objective of both MYL-GAI-3001 and MYL-GAI-3002 was to test whether MYL-1501D once daily is non-inferior to US-approved Lantus once daily. Secondary objectives included comparisons of MYL-1501D to US-Lantus at 24 weeks and at 52 weeks (MYL-GAI-3001 only) with respect to a variety of measures of glycemic control, immunogenicity, hypoglycemia, and insulin dose requirements.

Dr. Ketterman and Dr. Rauschecker both evaluated the demographics and baseline characteristics of the patients enrolled in MYL-GAI-3001 and MYL-GAI-3002. Some differences were observed between the two studies. Some of these differences reflect the patient populations (T1DM vs T2DM): for instance, the patients enrolled in MYL-GAI-3001 were younger, had lower BMI, and longer history of diabetes. In addition, the patients enrolled in MYL-GAI-3001 had better glycemic control at baseline (mean HbA1c 7.4% compared to 8.1% in the patients enrolled in MYL-GAI-3002). In MYL-GAI-3001, almost all of the patients were Caucasian (94.6%); in MYL-GAI-3002, about half of the patients were Caucasian (52.7%). About 40% of the patients enrolled in MYL-GAI-3001 were at US sites; about 80% of the patients enrolled in MYL-GAI-3002 were at US sites. While some differences were observed across the two studies, the distribution of patient demographics and baseline characteristics were well-balanced with each of the trials.

Dr. Ketterman and Dr. Rauschecker also both evaluated patient disposition in the pivotal trials. Overall, about 5% of the patients enrolled in MYL-GAI-3001 and about 11% of the patients enrolled in MYL-GAI-3002 did not have an HbA1c measurement at week 24.

Table 3: Patient Disposition in MYL-GAI-3001

Disposition	MYL IG n (%)	Lantus n (%)	Total n (%)	p-value
Patients randomized	**280**	**278**	**558**	
Patients completed the study	261 (93.2)	256 (92.1)	517 (92.7)	
Patients discontinued the study before or at Week 24	11 (3.9)	15 (5.4)	26 (4.7)	0.411
Reasons for study discontinuation before or at Week 24				
Adverse event	2 (0.7)	3 (1.1)	5 (0.9)	
Lost to follow-up	1 (0.4)	2 (0.7)	3 (0.5)	
Protocol deviation	4 (1.4)	3 (1.1)	7 (1.3)	
Withdrawal of consent	4 (1.4)	6 (2.2)	10 (1.8)	
Other	0	1 (0.4)	1 (0.2)	
Patients discontinued the study through end of study	19 (6.8)	22 (7.9)	41 (7.3)	0.610
Reasons for study discontinuation through end of study				
Adverse event	4 (1.4)	3 (1.1)	7 (1.3)	
Lost to follow-up	1 (0.4)	2 (0.7)	3 (0.5)	
Protocol deviation	7 (2.5)	9 (3.2)	16 (2.9)	
Withdrawal of consent	7 (2.5)	6 (2.2)	13 (2.3)	
Other	0	2 (0.7)	2 (0.4)	

Source: Table 10-1 from Sponsor's clinical study report

Table 4: Patient Disposition in MYL-GAI-3002

Disposition	MYL IG (N=277) n (%)	Lantus (N=283) n (%)	Total (N=560) n (%)	p-value
Patients completed study	240 (86.6)	250 (88.3)	490 (87.5)	
Patients discontinued study	37 (13.4)	33 (11.7)	70 (12.5)	0.544
Reason for study discontinuation				
Withdrawal of consent	12 (4.3)	13 (4.6)	25 (4.5)	
Protocol violation	10 (3.6)	7 (2.5)	17 (3.0)	
Adverse event	3 (1.1)	0	3 (0.5)	
Lost to follow-up	10 (3.6)	10 (3.5)	20 (3.6)	
The Investigator or the sponsor, for any reason, terminates the study prematurely[1]	1 (0.4)	0	1 (0.2)	
Other	1 (0.4)	3 (1.1)	4 (0.7)	

Source: Table 10-1 from the Sponsor's Clinical Study Report

Figure 5: Subjects with missing primary endpoint data (Week 24 HbA1c)

Study	All Subjects		MYL IG		Lantus	
	N	Missing (%)	n	Missing (%)	n	Missing (%)
3001	558	4.7	280	4.3	278	5
3002	560	11.4	277	11.6	283	11.3

Source: FDA Statistical Review

Dr. Ketterman employed different statistical methods than the Applicant to evaluate the primary endpoints of MYL-GAI-3001 and MYL-GAI-3002. Both Dr. Ketterman and the Applicant evaluated the primary endpoints in populations they defined as the "Intent-to-Treat (ITT) population. While the Applicant defined "ITT" to include only those patients who had at least one post-baseline observation and who received at least one dose of study drug, Dr. Ketterman defined the ITT population to include all randomized subjects. In addition, Dr. Ketterman used different methods to address the issue of missing data. The Applicant relied on analyses using a MMRM model and also sensitivity analyses using the last observation carried forward (LOCF) approach to address the issue of missing data; at the request of FDA, the Applicant also submitted analyses with imputations using the monotone regression method for weeks 12 and 16 and using the Markov Chain Monte Carlo (MCMC) approach at week 24. In contrast, Dr. Ketterman relied on a return to baseline multiple imputation approach to impute data for subjects who did not have an HbA1c measurement at week 24. Please see Dr. Ketterman's review for details regarding this return to baseline imputation approach. In addition, Dr. Ketterman conducted a tipping point analysis whereby a penalty was added to the imputed HbA1c value for patients in the MYL-1501D treatment arm missing a week 24 HbA1c. The penalty was gradually increased to determine the value necessary to result in a conclusion that MYL-1501D is inferior to US-approved Lantus.

Table 5: Primary Efficacy Analyses by Applicant and FDA for MYL-GAI-3001 and MYL-GAI-3002

Study Analytical Approach	Treatment Arm	Number of Subjects	Mean Baseline HbA1c (%)	LS Mean HbA1c Change from Baseline (95% CI)	LS Mean Treatment Difference: MYL IG vs. Lantus (95% CI)
3001 (T1DM)					
MMRM*	MYL IG	280	7.37	0.14 (0.03, 0.24)	0.03 (-0.66, 0.12)
	Lantus	277	7.39	0.11 (0.01, 0.22)	
Return to baseline ¶	MYL IG	280		0.11 (0.05, 0.18)	0.03 (-0.06, 0.12)
	Lantus	278		0.08 (0.02, 0.15)	
3002 (T2DM)					
MMRM*	MYL IG	274	8.14	-0.60 (-0.78, -0.41)	0.06 (-0.10, 0.22)
	Lantus	278	8.00	-0.66 (-0.84, -0.48)	
Return to baseline ¶	MYL IG	277		-0.37 (-0.49, -0.26)	0.05 (-0.11, 0.21)
	Lantus	283		-0.42 (-0.54, -0.31)	

Abbreviations: CI, confidence interval; MMRM, mixed-effect repeated measures model; HbA1c, hemoglobin A1c; LS, least squares; T1DM, type 1 diabetes; T2DM, type 2 diabetes; and vs, versus.
*Applicant's analysis of the primary efficacy endpoint. Note the number of subjects differs as in the Applicant's analysis, patients in the ITT population were excluded if they lacked post-baseline efficacy data
¶ Agency's reanalysis of the primary efficacy endpoint. This analysis includes subjects who were excluded from the Applicant's analysis.
Source: FDA Clinical Review (adapted from FDA Statistical Review)

As shown in **Table 5Error! Reference source not found.**, the FDA analyses of the primary endpoint support a conclusion that Process V MYL-1501D is non-inferior to US-approved Lantus. The MMRM analyses conducted by the Applicant also returned results that support this conclusion. The tipping point analyses determined that the penalty that needed to be added to the missing HbA1c values in the MYL-1501D treatment arm are 1.7% or more in MYL-GAI-3001 and 1% or more in MYL-GAI-3002 to reverse the conclusion of non-inferiority.

Dr. Ketterman also evaluated trends in prandial and basal insulin dose across treatment arms in MYL-GAI-3001 and basal insulin dose in MYL-GAI-3002. While Dr. Ketterman observed a small, nominally statistically significant difference between average MYL-1501D and average US-approved Lantus doses at time points after baseline in MYL-GAI-3001, the absolute differences observed in average insulin glargine doses across the treatment arms are clinically insignificant.

Dr. Ketterman also conducted subgroup analyses by sex, race, geographic region, and age. In some instances, the analyses were limited due to the size of the subgroups (e.g., non-Caucasians in MYL-GAI-3001). None of the subgroup analyses performed yielded results that suggested a treatment difference in the different subgroups.

8. Safety

Dr. Mitra Rauschecker conducted the safety analysis for MYL-1501D. The evaluation was limited to the clinical data from the two Phase 3 trials (MYL-GAI-3001 and MYL-GAI-3002). Dr. Rauschecker concluded, and I concur, that the safety findings for the two trials showed similar safety profiles for Process V MYL-1501D and US-approved Lantus and that the findings were consistent with the known safety profile of the listed drug (US-approved Lantus). Because the Phase 3 trials used Process V MYL-1501D rather than Process VI MYL-1501D (the to-be-marketed product), sufficient clinical information to support a scientific bridge between Process VI MYL-1501D and Process V MYL-1501D is necessary for FDA to rely on the data from MYL-GAI-3001 and MYL-GAI-3002 to make a conclusion about the safety of Process VI MYL-1501D.

The overall exposure to MYL-1501D met the recommendations made by FDA at the End-of-Phase 2 meeting (FDA recommended that the Phase 3 trials should enroll at least 500 patients with T1DM and 560 patients with T2DM). In MYL-GAI-3001, 280 patients with T1DM were exposed to MYL-1501D with a mean (SD) duration of exposure to MYL-1501D of 351 days (± 60 days). In MYL-GAI-3002, 276 patients with T2DM were exposed to MYL-1501D with a mean (SD) duration of exposure to MYL-1501D of 157 days (± 39 days).

There were three deaths reported in MYL-GAI-3001 (2 in the MYL-1501D treatment arm and 1 in the US-approved Lantus treatment arm). At least one of the deaths in the MYL-1501D treatment arm was due to hypoglycemia. No deaths were observed in MYL-GAI-3002. Dr. Rauschecker concluded, and I concur, that the deaths observed in MYL-GAI-3001 do not suggest any particular concern: while hypoglycemia may have contributed to these events, such events are unfortunately expected in this population.

The frequency of serious adverse events (SAEs) observed in the Phase 3 trials was similar across treatment arms. A total of 40 SAEs were observed in MYL-GAI-3001 (18 in the MYL-1501D treatment arm and 22 in the US-approved treatment arm) and 17 SAEs observed in MYL-GAI-3002 (8 in the MYL-1501D treatment arm and 9 in the US-approved Lantus treatment arm). The most common serious adverse event was hypoglycemia (2.5% in the MYL-1501D treatment arm compared to 3.6% in the US-approved Lantus treatment arm in MYL-GAI-3001; 0% in the MYL-1501D treatment arm compared to 0.4% in the US-approved Lantus treatment arm in MYL-GAI-3002).

Dr. Rauschecker reviewed events of hypoglycemia, focusing on events of severe hypoglycemia (defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions which results in neurological recovery) reported in the Phase 3 trials. Overall, events of hypoglycemia (including severe hypoglycemia) were balanced across treatment arms in both trials.

Table 6: Hypoglycemia Adverse Events in MYL-GAI-3001

Hypoglycemia Adverse Events	Lantus (n=278)		Mylan IG (n=280)	
Subjects with Hypoglycemia Events	269	96.8%	273	97.5%
Documented Symptomatic	249	89.6%	249	88.9%
-Severe	13	4.7%	11	3.9%
Episodes of Severe Hypoglycemia Subjects by number of episodes	20	-	14	-
-1 episode	10	-	9	-
-2 episodes	2	-	1	-
-3 episodes	0	-	1	-
-4-6 episodes	1	-	0	-
Time to first event of Severe Hypoglycemia (Days)				
Mean	183.6		64.4	
Median	166.0		72.0	
Min	6.0		3.0	
Max	360.0		166.0	

Source: FDA Clinical Review

Table 7: Hypoglycemia Adverse Events in MYL-GAI-3002

Hypoglycemia Adverse Events	Lantus (n=282)		Mylan IG (n=276)	
Subjects with Hypoglycemia Events	136	48.2%	130	47.1%
Documented Symptomatic	76	27.0%	75	27.2%
-Severe	1	0.4%	0	0.0%

Source: FDA Clinical Review

Dr. Rauschecker also reviewed the frequency of all TEAEs in the phase 3 trials. The incidence and distribution of TEAEs were similar across treatment arms in both trials. Immunogenicity was an important consideration in Dr. Rauschecker's safety review. The Applicant analyzed anti-drug antibodies (ADAs) using a two-assay approach (the assays were identical with the exception of a radiolabeled tracer for MYL-1501D and US-approved Lantus. Total anti-drug antibody and insulin cross reactivity results were reported in terms of their presence (positive or negative), along with the percent specific binding (%SB). Drug-specific ADAs were determined by gamma counting of ADA complex formation and is expressed as a percentage of bound to total radioactivity (%B/T).

In MYL-GAI-3001, about 73% of patients were positive for ADA at baseline in both treatment arms. In MYL-GAI-3002, about 19% of patients in the MYL-1501D treatment arm and 21% of patients in the US-approved Lantus treatment arm were positive for ADA at baseline. For both trials, the incidences of positive responses for total ADA and insulin cross-reactive antibodies were similar between treatment groups at all scheduled visits for both assays.

No differences between treatment groups in MYL-GAI-3001 were reported with regards to ADA or insulin cross-reactive antibody formation. For MYL-GAI-3002, small but nominally statistically significant increases in both ADA and insulin cross-reactive antibody formation was observed in the MYL-1501D treatment arm relative to the US-approved Lantus treatment

arms using the MYL-1501D assay. It is unclear whether the observed differences in MYL-GAI-3002 were due to differences in the baseline prevalence of ADA across treatment arms, due to chance, or due to a difference in the immunogenicity of the two insulin glargine products. Dr. Rauschecker concluded, and I agree, that the small observed differences did not suggest a clinically important difference.

Table 8: Proportion of Subjects with Positive Total Anti-Drug and Insulin Cross-Reactive Antibodies in MYL-GAI-3001

	MYL IG Assay			Lantus Assay		
	MYL IG N=280	Lantus N=278	p-value	MYL IG N=280	Lantus N=278	p-value
Total Anti-Drug antibodies						
Baseline Positive	205 (73.2)	205 (73.7)	0.923	209 (74.6)	221 (79.5)	0.355
Week 12 Positive	204 (72.9)	200 (71.9)	>0.999	203 (72.5)	208 (74.8)	0.226
Week 24 Positive	194 (69.3)	197 (70.9)	0.765	209 (74.6)	206 (74.1)	0.834
Week 36 Positive	184 (65.7)	179 (64.4)	0.918	191 (68.2)	183 (65.8)	0.830
Week 52 Positive	190 (67.9)	185 (66.5)	0.833	196 (70.0)	190 (68.3)	>0.999
Insulin cross-reactive antibodies						
Baseline Positive	204 (72.9)	211 (75.9)	0.431	201 (71.8)	217 (78.1)	0.196
Week 12 Positive	205 (73.2)	200 (71.9)	>0.999	198 (70.7)	203 (73.0)	0.238
Week 24 Positive	194 (69.3)	200 (71.9)	0.548	200 (71.4)	198 (71.2)	0.920
Week 36 Positive	188 (67.1)	178 (64.0)	0.755	186 (66.4)	175 (62.9)	0.605
Week 52 Positive	189 (67.5)	186 (66.9)	>0.999	188 (67.1)	181 (65.1)	0.918

Source: FDA Clinical Review (adapted from Applicant CSR for MYL-GAI-3001)

Table 9: Proportions of Subjects with Positive Total Anti-Drug and Insulin Cross-Reactive Antibodies in MYL-GAI-3002

	MYL IG Assay			Lantus Assay		
	MYL IG N=276	Lantus N=282	p-value	MYL IG N=276	Lantus N=282	p-value
Total Anti-Drug antibodies						
Baseline Positive	53 (19.2)	60 (21.3)	0.598	61 (22.1)	66 (23.4)	0.687
Week 12 Positive	61 (22.1)	64 (22.7)	0.918	69 (25.0)	71 (25.2)	>0.999
Week 24 Positive	70 (25.4)	76 (27.0)	0.693	75 (27.2)	77 (27.3)	0.922
Insulin cross-reactive antibodies						
Baseline Positive	57 (20.7)	59 (20.9)	>0.999	63 (22.8)	65 (23.0)	0.920
Week 12 Positive	60 (21.7)	62 (22.0)	>0.999	61 (22.1)	65 (23.0)	0.760
Week 24 Positive	72 (26.1)	72 (25.5)	0.921	70 (25.4)	70 (24.8)	>0.999

Source: FDA Clinical Review (adapted from Applicant CSR for MYL-GAI-3002)

9. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

10. Pediatrics

The Division determined that this NDA does not trigger the Pediatric Research Equity Act. Therefore, no pediatric studies under PREA are recommended.

11. Labeling

Ariane Conrad, Pharm D, conducted a review of the proposed labels and labeling and the human factors (HF) validation study report. DMEPA had provided advice to the Applicant at the End-of-Phase 2 meeting, recommending a human factors validation study.

The HF validation studies (one in an adult population and one in a pediatric population) were designed to demonstrate that the intended users understand the Instructions for Use (IFU) and can prepare and administer doses of MYL-1501D with the pen injector. The review of the HF study report found that the untrained pen naïve pediatric patient group did not have the minimum of 15 patients, consistent with prior advice provided for the adult study to include at least 15 patients in each user group. For that reason, DMEPA has identified the need for additional information from pediatric uses as a deficiency in the NDA submission.

The DMEPA review identified deficiencies with the proposed IFU. The proposed IFU should be modified before the Applicant repeats the HF validation study with 15 untrained injection naïve pediatric patients.

In addition, DMEPA found that the product differentiation study showed that study participants failed to select the Semglee pen. DMEPA has provided specific recommendations for modifications to the carton and container labeling to enhance product differentiation. Once the Applicant has implemented these modifications and any other labeling changes considered necessary, the Applicant should conduct a differentiation study with the intended user population for the product with at least 15 uses in each group.

The review identified deficiencies with the proposed labeling and recommendations to address these deficiencies will be communicated to the Applicant in the CRL. However, FDA will reserve additional comments on the proposed labeling until the application is otherwise adequate.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Based on my review of the data submitted to the NDA, I recommend issuing a **Complete Response**.

In addition to the clinical deficiencies known at the time of filing (e.g., the additional clinical safety and efficacy data needed to support a scientific bridge between Process VI MYL-1501D and Process V MYL-1501D based on the specific manufacturing changes made; the lack of PK/PD comparability data necessary to support the bridging between Process VI MYL-1501D in vials compared to Process VI MYL-1501D in cartridges), other deficiencies were identified

during the review, including various product quality deficiencies (e.g., objectionable conditions observed at a manufacturing facility, deficient antimicrobial effectiveness testing (AET), lack of AET data supporting product expiry) and labeling deficiencies (including the prescribing information, the carton and container labeling, and the Instructions for Use). As a result of the identified deficiencies, I am unable to conclude that there is a favorable Benefit-Risk assessment for the proposed to-be-marketed (i.e., Process VI) drug product.

See Complete Response Letter for specific deficiencies.

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

/s/

PATRICK ARCHDEACON
05/17/2018

WILLIAM H CHONG
05/17/2018
I agree with Dr. Archdeacon's assessment and recommendations.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210605
Priority or Standard	Standard
Submit Date(s)	August 31, 2017
Received Date(s)	August 31, 2017
PDUFA Goal Date	May 17, 2018
Division/Office	OND/ODE-II/DMEP
Reviewer Name(s)	Mitra Rauschecker
Review Completion Date	April 30, 2018
Established/Proper Name	Insulin glargine
(Proposed) Trade Name	Semglee
Applicant	Mylan
Dosage Form(s)	Subcutaneous injection
Applicant Proposed Dosing Regimen(s)	Individualized
Applicant Proposed Indication(s)/Population(s)	Improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Adults and pediatric patients with type 1 diabetes mellitus and adults with type 2 diabetes mellitus

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Glossary

ADA	Anti-drug antibodies
AE	Adverse Event
AIA	Anti-Insulin Antibody
Anti-HCP	Anti-host cell protein
β-cell	Beta-Cell
BL	Baseline
BMI	Body Mass Index
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CSR	Clinical Study Report
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complication Trial
DMEP	Division of Metabolism and Endocrinology Products
DMEPA	Division of Medication Error Prevention and Analysis
DPP-4	Dipeptidyl Peptidase-4
ECG	Electrocardiogram
E. coli	Escherichia coli
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GLP-1	Glucagon-like peptide 1
HbA1c	Hemoglobin A1c (Glycosylated Hemoglobin)
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IU	International Units

ITT	Intention to Treat
KG	Kilogram
LOCF	Last observation carried forward
MDRD	Modification in Diet and Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect repeated measure model
NAb	Neutralizing Antibody
NI	Non-inferiority
NDA	New Drug Application
OADs	Oral antidiabetic drugs
OBP	Office of Biotechnology Products
OSI	Office of Scientific Investigation
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
PREA	Pediatric Research Equity Act
PT	Preferred Term
REML	Restricted maximum likelihood
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SC	Subcutaneous
SGLT-2	Sodium-Glucose Cotransporter 2
SMBG	Self-monitored blood glucose
SMQ	System MedDRA Query
SOC	System Organ Class
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
US	United States

1. Executive Summary

1.1. Product Introduction

Mylan's Semglee (MYL-1501D), hereafter referred to as MYL IG, is a proposed insulin glargine product that intends to rely, in part, on the Agency's finding of safety and effectiveness for Lantus (insulin glargine), the listed drug manufactured by Sanofi-Aventis. MYL IG is a long-acting insulin analog, administered via subcutaneous injection once daily, and acts to lower blood glucose levels. The amino acid sequence of MYL IG is identical to that of Lantus, while both differ from native human insulin by three amino acid residues, which allows insulin glargine to have a slow, stable release into the systemic circulation. MYL IG is produced using recombinant strain of the yeast *Pichia pastoris*, while Lantus is produced using recombinant *Escherichia coli*[1].

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has submitted a 505(b)(2) application for MYL IG, which relies, in part, on the FDA's finding of safety and effectiveness for the listed drug Lantus (insulin glargine). In order to establish that such reliance is scientifically justified, the Applicant has submitted comparative analytical testing intended to demonstrate sufficient analytical similarity to Lantus[1], pharmacokinetic/pharmacodynamic (PK/PD) data intending to show PK/PD similarity to Lantus, and comparative clinical data intended to evaluate the impact of immunogenicity, if any, on the safety and efficacy profile of MYL IG and to demonstrate sufficient similarity to Lantus with regard to safety and efficacy. The adequacy of these data is discussed in this review and in the CDTL memo for this application.

1.3. Benefit-Risk Assessment

[1] In this review 'Lantus' refers to U.S.-approved Lantus. EU-approved Lantus will be referred to as 'EU-approved Lantus' in this review.

Benefit-Risk Integrated Assessment

Diabetes mellitus is a condition of impaired glucose metabolism that results in hyperglycemia, and is increasingly common in the United States. There are two types of diabetes; type 1 diabetes (T1DM) is distinguished by absolute insulin deficiency that is the result of autoimmune destruction of pancreatic beta cells; and type 2 diabetes (T2DM), which is characterized by either insulin resistance or a deficiency of insulin. Both types of diabetes increase the risk for both microvascular and macrovascular complications. Insulin treatment is required for patients with T1DM, and is often necessary for patients with T2DM after having failed multiple non-insulin antihyperglycemic medications[2].

The Applicant has submitted a new drug application through the 505(b)(2) pathway for Semglee (MYL IG), an insulin glargine product that relies, in part, on the FDA's finding of safety and effectiveness for Lantus (insulin glargine injection), the listed drug manufactured by Sanofi-Aventis. The drug substance used in the Phase 3 clinical studies was manufactured at Biocon's (the Applicant's development partner) manufacturing site in India using Process V. In 2014, the Applicant notified the FDA of the decision to transfer manufacturing of the drug substance to Biocon's facility in Malaysia using Process VI, after the European Medicines Agency (EMA) advised the Applicant to reduce (b) (4). The use of Process VI reduces (b) (4) of the drug substance, and enables scaling up of the manufacturing for commercial production of the drug substance. The Applicant conducted comparability studies, along with comparative toxicity studies, and PK/PD studies between the drug substances produced by Process V and studied in the Phase 3 trials, and the drug substance produced by Process VI which the Applicant intends to market, but did not conduct additional clinical studies to evaluate for potential differences in immunogenicity between the products produced by the two Processes. The manufacturing change is considered substantial and the reviewers from OPQ/ONDP concluded that analytical similarity data would not be sufficient to rule out a potential clinical impact from these manufacturing changes. In fact, it is expected that clinical differences between the Process V and Process VI products are likely, given that the Process VI product has a lower concentration of (b) (4), and there were changes to the stability and impurity profiles. As such, the clinical data that the Applicant intends to rely on for labeling may not truly represent what would be expected from the marketed product. For this reason, the Agency initially refused-to-file the NDA, but the Applicant filed the application over protest. It is important to note that the current clinical review was conducted with the knowledge that there were important clinical bridging data lacking from the application. With this submission, the Applicant has submitted data from two Phase 3 trials, one (Trial 3001) which studied MYL IG manufactured using the Process V in addition to prandial insulin in subjects with T1DM, and the second (Trial 3002) which studied MYL IG manufactured using the Process V in addition to non-insulin antihyperglycemic medications in subjects with T2DM, both in comparison to Lantus. Data from the two Phase 3 clinical trials demonstrated that MYL IG manufactured using the Process V is non-inferior to Lantus for the primary endpoint of mean change of HbA1c from baseline to Week 24 and support the conclusion that reliance on the FDA's finding of safety and effectiveness for the

listed drug Lantus is scientifically justified. The safety findings were consistent with the previously observed safety profile of Lantus, while the immunogenicity data demonstrated no clinically important differences between Lantus and MYL IG. Whereas the Applicant conducted studies of MYL IG using drug product manufactured using Process V, the to-be marketed drug product is manufactured using Process VI. As insulin is a protein product, potential differences in overall impurity profile, higher order species, amino acid sequence, and stability introduced by manufacturing changes can result in the potential for antibody formation, and therefore a potential effect on both efficacy and safety. As the drug substance produced by Process VI has not been evaluated in clinical bridging studies to evaluate for potential differences in immunogenicity, the data submitted by the Applicant is incomplete, and the potential impact of the manufacturing change is unknown. Due to concerns about the potential for differences between the drug products generated by these two Processes (including differences in immunogenicity), this reviewer recommends issuing a complete response to the NDA.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diabetes mellitus is a serious chronic medical condition characterized by hyperglycemia, and includes two main types; T1DM and T2DM. • T1DM is caused by autoimmune destruction of the pancreatic beta cells, which leads to impaired insulin production and secretion, and impaired glucose metabolism. • T2DM is characterized by hyperglycemia either due to insulin resistance or a deficiency of insulin, and is often associated with other metabolic derangements, such as dyslipidemia, hypertension, and obesity. • Diabetes mellitus affects nearly thirty million people in the United States, the majority (90-95%) of these patients have T2DM, according to the Centers for Disease Control (CDC)[3]. • Acute life-threatening complications of T1DM include diabetic ketoacidosis due to insulin deficiency, while chronic complications	Both T1DM and T2DM are serious, life-threatening conditions that can lead to serious morbidity and mortality if left untreated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of both T1DM and T2DM include cardiovascular disease, retinopathy, nephropathy, and neuropathy.	
Current Treatment Options	• The results of the Diabetes Control and Complications Trial (DCCT)[4,5,6] demonstrated that intensive insulin therapy resulted in improved glycemic control as measured by HbA1c, which was associated with improved clinical outcomes in patients with T1DM. • Due to the depletion of pancreatic beta cells which produce insulin, patients with T1DM require exogenous insulin for survival. Pramlintide, an amylin-mimetic, is also approved as adjunctive therapy to insulin. • Treatment options for T2DM includes lifestyle modifications, usually followed by the addition of one or multiple different medications[7]. There are currently multiple classes of pharmacologic treatments for T2DM, with multiple members of each class, including biguanides, sulfonylureas, insulin and insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose linked transporter (SGLT)-2 inhibitors.	Intensive insulin therapy is the standard of care for patients with T1DM. Patients with T2DM often require multiple agents for glycemic control, and due to the progressive nature of the disease, may also require insulin to achieve glycemic targets.
Benefit	• The Applicant is relying, in part, on FDA's finding of safety and effectiveness for the listed drug Lantus. Comparative clinical data from Trial 3001 (T1DM subjects) and Trial 3002 (T2DM subjects) demonstrated that MYL IG in combination with other antihyperglycemic agents (prandial insulin in Trial 3001 and oral antihyperglycemic agents in Trial 3002) was non-inferior to Lantus in change in HbA1c from baseline to Week 24.	The Phase 3 clinical trials for MYL IG generated by Process V support the conclusion that MYL IG is non-inferior to Lantus in patients with T1DM and T2DM and support the reliance on FDA's finding of safety and effectiveness for the listed drug, Lantus.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The risks identified for MYL IG during the Phase 3 studies were similar to the previously identified risks associated with Lantus use. No new safety signals were identified for the MYL IG produced by Process V. The to-be-marketed drug product manufactured using Process VI has not been evaluated in clinical trials.	The risks associated with the Process VI product are unknown. Additional clinical safety and efficacy bridging data are required to determine whether the data generated using Process V is applicable to the Process VI product.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is a serious chronic medical condition characterized by hyperglycemia, and includes two main types of diabetes; T1DM and T2DM. T1DM is caused by T-cell mediated autoimmune destruction of the pancreatic β-cells, which results in impaired insulin production and secretion, and which may lead to acute life-threatening complications of T1DM including diabetic ketoacidosis. T2DM is either due to insulin resistance or a deficiency of insulin, and is often associated with other metabolic derangements, such as dyslipidemia, hypertension, and obesity. Chronic complications of diabetes include cardiovascular disease, retinopathy, nephropathy, and neuropathy.

The DCCT demonstrated intensive insulin therapy resulted in improved glycemic control as well as improved outcomes[4,5,6]. As a result, patients with T1DM are recommended to use multiple daily doses of insulin, including "basal" or long-acting insulin, along with "prandial" or short-acting insulin taken before each meal, to achieve HbA1c goals. An insulin pump, using a continuous subcutaneous infusion of short-acting insulin, may also be used. Due to the progressive nature of the disease, many patients with T2DM may also require insulin to achieve glycemic targets. Basal insulin is the most common initial insulin therapy in patients with T2DM.

2.2. Analysis of Current Treatment Options

Current approved medical therapies for T1DM include exogenous insulin and insulin analogues, which are associated with a risk of hypoglycemia, along with adjunctive therapy with pramlintide, an amylin-mimetic. As patients with T1DM have a deficiency of insulin due to a lack of functional pancreatic beta cells, they depend on exogenously administered insulin for survival. Lifestyle modifications, including diet and exercise, are first-line treatments for T2DM, however, the majority of patients require pharmacologic treatments. There are currently 12 different classes of medications approved by the Food and Drug Administration (FDA) to treat T2DM, either as monotherapy or in combination. Many drug classes have multiple members of

the class approved.

- Biguanides
  - Metformin
- Sulfonylureas
  - Glimepiride, Glipizide, Glyburide, Chlorpropamide, Tolazamide, Tolbutamide
- Thiazolidinediones
  - Pioglitazone, Rosiglitazone
- Meglitinides
  - Repaglinide, Nateglinide
- Alpha-glucosidase inhibitors
  - Acarbose; Meglitol
- Amylin mimetics
  - Pramlintide
- Dopamine agonists
  - Bromocriptine
- Insulin and insulin analogues
  - Insulin regular, Insulin detemir, Insulin glargine, Insulin glulisine, Insulin aspart, Insulin isophane (NPH), Insulin lispro, Insulin degludec
- Bile acid sequestrants
  - Colesevelam
- GLP-1 analogues
  - Exenatide, Dulaglutide, Albiglutide, Liraglutide, Lixisenatide
- DPP-4 inhibitors
  - Sitagliptin, Alogliptin, Saxagliptin, Linagliptin
- SGLT-2 inhibitors
  - Dapagliflozin, Empagliflozin, Canagliflozin,

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

MYL IG is not currently marketed in the United States. The listed drug, Lantus, was approved in

April 2000, and is currently marketed in the United States and in the EU, among other countries, and is available by prescription.

3.2. Summary of Presubmission/Submission Regulatory Activity

A summary of relevant dates of regulatory activity in the MYL IG development program are listed below.

- December 14, 2011: IND 105279 opened by Biocon SA
- October 22, 2012: Type C written response guidance provided by FDA
- August 21, 2013: Sponsorship of IND transferred from Biocon to Mylan
- March 7, 2014: End of Phase 2 meeting to discuss the Phase 3 clinical program. The Applicant also discussed their intent to transfer manufacturing of the drug substance from Process V (manufacturing site in India), to Process VI (manufacturing site in Malaysia). The FDA advised that additional nonclinical and/or clinical studies may be required in support of any difference in quality attributes.
- August 31, 2015: Amended clinical protocols for Trials 3001 and 3002 submitted to IND
- February 24, 2016: Type C written response to discuss comparability plans to bridge the drug substance and product produced using Process V and used in the clinical trials to the to-be marketed drug product and substance manufactured using Process VI. The FDA advised that there were substantial differences between the manufacturing processes at the two facilities, and the comparability study may find additional differences that could have an impact on safety or efficacy profiles. The Applicant was advised that the FDA did not agree to the proposal to submit the NDA for the to-be-marketed product (Process VI) with only analytical comparability.
- April 7, 2016: FDA responded to the Applicant's request for clarification regarding the previously issued written responses. The FDA reiterated that although Process VI manufacturing process reduced (b) (4) of the drug substance, potential differences in additional quality attributes, and therefore potential impact on efficacy, safety, and immunogenicity, may be found once the comparability study is completed. The FDA also reiterated that the NDA should not be submitted for the Process VI product with only analytical comparability, and recommended that the Applicant submit its NDA for the Process V product.
- Nov. 10, 2016: Type C written responses regarding the completed comparability studies. The FDA requested additional studies, including a subchronic bridging toxicology study comparing Process VI formulation with the listed drug, Lantus. Additionally, the FDA recommended that a PK/PD study be conducted to compare Process VI product with Process V product and Lantus. Additionally, the Applicant was informed an immunogenicity risk assessment would need to be completed by the Office of Biotechnology Products (OBP). However, the sponsor submitted the NDA before this

immunogenicity assessment was completed.

- April 27, 2017: the Applicant submits the NDA for the to-be marketed Process VI product.
- June 26, 2017: the FDA notifies the Applicant of the decision to Refuse to File the NDA, as it was determined to be not sufficiently complete to permit a substantive review. The lack of clinical safety and efficacy (including immunogenicity assessment) bridging data to bridge the process V and process VI formulations was cited. In addition, it was noted that it was unclear from the top line results if PD similarity between the Process V product and Lantus in the MYL-1501D-1001 study had been demonstrated.
- August 15, 2017: Type A meeting to discuss the FDA's Refusal to File the NDA. The FDA reiterated its reasoning behind the decision to Refuse to File had not changed. The Applicant was informed that it could proceed to request the application be Filed Over Protest, and the Division of Metabolism and Endocrinology Products (DMEP) would be obligated to review the application under a standard review timeline. The Applicant was encouraged to submit a draft protocol for a requested 18-week clinical bridging study (bridging the Process V and Process VI products) to the corresponding IND.
- August 31, 2017: The Applicant requests the NDA be Filed over Protest.
- September 19, 2017: The Applicant submits the clinical protocol for the requested 18-week clinical bridging study entitled "A Randomized, Multi-center, Double-Blind, Parallel-Group Clinical Study Comparing the Efficacy and Safety of MYL-1501D Produced by Two Manufacturing Processes in Type 1 Diabetes Mellitus Patients" to the corresponding IND.

3.3. Foreign Regulatory Actions and Marketing History

Mylan's MYL IG has been approved for marketing in Guatemala, Guyana, Macau, Nigeria, Paraguay, Uganda and Zimbabwe for the treatment of diabetes mellitus in adults, adolescents and children aged 6 years and above.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division requested the Office of Scientific Investigations (OSI) conduct clinical inspections for three domestic and two foreign clinical study sites involved in the two Phase 3 clinical trials. These sites were selected on the basis of high subject enrollment, history of prior inspections by OSI or other regulatory agencies, lack of audit history by the Applicant, and protocol

violations. Since many of the highest enrolling sites had already been inspected for other applications, they were not chosen. Inspections were primarily focused on review of informed consent documents, institutional review board (IRB) and ethics committee correspondences, Form 1572s, financial disclosures, training records, curriculum vitae and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, and subject source documents, including medical history records, drug accountability, concomitant medication records, and adverse event reports. There were no regulatory violations revealed after inspections of both the clinical investigator and sites, as well as inspections of the Applicant. Overall, the inspectional findings support the validity and reliability of the clinical data submitted by the Applicant. For further details, please see Dr. Cynthia Kleppinger's review, dated March 14, 2018.

4.2. Product Quality

MYL IG is a recombinant insulin glargine product produced using *Pichia pastoris*. Insulin glargine is an insulin analog that is composed of 53 amino acids arranged in 2 chains which are connected by 2 disulfide linkages and that differs from human insulin by three amino acid residues. MYL IG has an identical primary structure to that of Lantus, an approved recombinant insulin glargine product marketed by Sanofi Aventis.

The CMC review for this Application was conducted by Drs. Muthukumar Ramaswamy (Application Technical Lead, Division of New Drug Products II [DNDPII]/Office of New Drug Products [ONDP]), Anika Lalmansingh (Regulatory Business Process Management I [RBPMI]/Office of Program and Regulatory Operations [OPRO]), Joseph Leginus (Division of New Drug Active Pharmaceutical Ingredient [DNDAPI]/ONDP), Donna Christner (DNDAPI/ONDP), Danae Christodoulou (DNDPII/ONDP), JoAnne Wang (Division of Process Assessment [DPAIII]/Office of Process and Facilities [OPF]), Chengjiu Hu (DPAIII/OPF), Vidya Pai (Division of Inspectional Assessment [DIA]/OPF), Brian J Ryan (DIA/OPF), Juandria Williams (DIA/OPF), Jennifer Patro (Division of Microbiology Assessment [DMA]/OPF), and Elizabeth Bearr (DMA/OPF).

The overall recommendation from the Office of Pharmaceutical Quality (OPQ) is a Complete Response. This was based on several issues related to the commercial manufacturing facility, which was found to have objectionable conditions observed, as well as concerns with the microbiological control of the product. In her facilities review, Dr. Pai notes several corrective actions to be taken by the Applicant including (b) (4) (b) (4). These corrective actions are required in order for the facility to be considered as acceptable to support the NDA. For further details, please refer to the Integrated CMC review from OPQ, the Facility Review by Dr. Vidya Pai, and the Microbiology Review by Dr. Jennifer Patro (see Section 4.3).

4.3. Clinical Microbiology

The Clinical Microbiology reviewer for this application was Dr. Jennifer Patro (Division of Microbiology Assessment [DMA]/OPF). Her recommendation is a Complete Response. Dr. Patro noted the following deficiencies in her review: lack of method suitability data for endotoxin, sterility, and antimicrobial effectiveness testing (AET), and lack of AET data supporting the product expiry from stability. For further details, please refer to the Microbiology Review.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology program conducted by the Applicant included 3 single dose toxicity studies, 1 skin-tolerance test, as well as 3 repeat dose toxicity studies. The Applicant is relying on the FDA's finding of safety and effectiveness for the listed drug, Lantus, with respect to carcinogenicity, mutagenicity, teratogenicity, fertility, and juvenile studies. Nonclinical information in published literature was also submitted in support of this application. Two of the repeat dose toxicity studies were comparative studies; one comparing MYL IG, US Lantus, and EU Lantus (Study G11066), as well as a second study comparing MYL IG produced by Process V, MYL IG produced by Process VI, and US Lantus (Study U-16176). In these studies, the toxicology profiles of MYL IG were similar to Lantus, and there were no unexpected toxicological observations for MYL IG. For further details on the nonclinical pharmacology/toxicology studies conducted in support of this application, please refer to the review by Dr. Arulasanam Thilagar.

4.5. Clinical Pharmacology

The Applicant conducted two Phase 1 clinical pharmacology studies to assess the PK/PD similarity between MYL IG and Lantus. One study, GLARGCT100111 was a 3- way crossover design, euglycemic clamp study in T1DM subjects to evaluate the PK/PD similarity of MYL IG process V, Lantus (US-approved), and EU-approved Lantus. The data with EU-approved Lantus are not considered relevant to the assessment of the safety and effectiveness of MYL IG, but were intended by the sponsor to provide the clinical pharmacology component of a bridge between Lantus (US) and EU-approved Lantus in the case that EU-approved Lantus was used in the Phase 3 studies as a comparator. However, only Lantus (US) was used in the Phase 3 studies as comparator. The second study, MYL-1501D-1001, was also a crossover design, euglycemic clamp study in T1DM subjects to evaluate the PK/PD similarity between MYL IG produced by Process V (MYL IG_V), MYL IG produced by Process VI (MYL IG_{VI}), and Lantus approved in the US (Lantus-US). The only primary endpoint in the MYL-1501D-1001 study was a PK endpoint (AUC_{0-24}), which met the 90% CI. However, the 90% CI was not met for several PD endpoints to demonstrate similarity between MYL IG_V and Lantus-US ($AUC_{GIR\ 0-24,}$ $AUC_{GIR\ 0-12}$, and $AUC_{GIR12-24}$), as well as to demonstrate similarity between MYL IG_{VI} and Lantus-US ($AUC_{GIR0-12}$), and MYL IG_V and MYL IG_{VI} ($AUC_{GIR0-12}$, $AUC_{GIR12-24}$). For interpretation of the clinical pharmacology studies

submitted by the Applicant, please refer to the Clinical Pharmacology Review by Dr. Jing Niu.

4.6. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health (CDRH) was consulted to evaluate the safety and functionality of the proposed pre-filled pen injector submitted by the Applicant. The performance of the device was evaluated for dose accuracy, functional performance, and biocompatibility of non-primary closure components. The submitted pre-filled pen device contains a total of 300 units of insulin glargine (3 mL of 100 U/ml), and is designed to administer up to 80 units of insulin glargine per subcutaneous injection. The CDRH reviewer was Dr. Rong Guo, who recommends approval based on review of the device constituent of the combination product.

4.7. Consumer Study Reviews

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted to review the human factors validation study reports, the differentiation study to assess differentiation between Mylan's pen and Lilly's Humulin R U-500 Kwikpen (due to the similar appearance of the two pens), and the proposed labeling submitted by the Applicant in support of this application. The Applicant conducted two human factors validation studies, one in an adult population and one in a pediatric population. The DMEPA found deficiencies with the human factors validation study, including an insufficient number of pediatric patients in the pediatric study, and are recommending the Applicant conduct an additional human factors validation study with pediatric patients. Additional deficiencies were also identified for the product insert, instructions for use, carton, and container labeling, and were based on safety concerns related to prior experience with other insulin products. The Applicant is also recommended to conduct a differentiation study to demonstrate the products can be differentiated by all the intended user groups once the carton and container labeling changes that are recommended have been implemented. Please see the Label and Labeling and Human Factors Results Review by Dr. Ariane Conrad for further details.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant conducted two Phase 1 PK/PD studies and two Phase 3 clinical trials to evaluate the safety and efficacy, of MYL IG in both T1DM and T2DM subjects. GLARGCT100111 was a single-dose PK/PD 3-way bridging study intended to show PK/PD similarity among Lantus, EU-Lantus, and MYL IG. Two Phase 3 clinical studies were conducted with MYL IG in order to evaluate the potential for immunogenicity, due to the formation of insulin antibodies. These antibodies could have an impact on both safety, and efficacy, as insulin antibodies could potentially lead to the need for dose alterations or increase the risk for hypoglycemia. Given the change in manufacturing from Process V to Process VI for MYL IG, the Applicant conducted the additional single-dose 3-way crossover euglycemic clamp study (MYL-1501D-1001) to demonstrate PK/PD similarity among MYL IG produced by Process V, MYL IG produced by Process VI, and Lantus. See Table 1, below. The Applicant also conducted several supportive studies in Japan, including a PK/PD study and a clinical efficacy and safety study of MYL IG versus Japan-approved Lantus (studies not listed below). The Japanese studies were supportive only and will not be discussed further as the data were not provided for review.

Reviewer comment: While the Applicant conducted MYL-1501D-1001 to provide a clinical bridge from the Process V drug product to the Process VI drug product, a single-dose euglycemic clamp study cannot evaluate potential differences in the immunogenicity of the two products nor can it adequately assess for potential differences in clinical and safety outcomes due to differences in impurities between the two products. As discussed earlier in Section 1.3 and Section 3.2, the Applicant was informed in its Refuse-to-File determination that the Agency had identified the lack of adequate bridging data from Process V to Process VI as a critical deficiency in the application. The Applicant, however, requested that the NDA be Filed over Protest.

Table 1: Clinical Studies in the MYL IG Development Program

NCT no./Study ID	Trial Design/Objectives	Regimen/ schedule/ route	Study Endpoints	Study Population	Treatment Duration/ Follow Up	No. of patients enrolled
Phase 1 PK/PD Studies						
GLARGCT100111	Single center, randomized, double-blind, single-dose, 3-way crossover euglycemic clamp study	Single dose of 0.4 IU/kg of MYL IG SC vs. Lantus-US SC and Lantus-EU SC at 3 separate visits	1°: compare PK/PD properties of MYL IG vs Lantus-US and Lantus-EU	T1DM subjects	3 single doses with a washout period of 5-28 days between doses	114 randomized, 112 completed

MYL-1501D-1001	Two center, randomized, double-blind, single-dose, 3-way crossover euglycemic clamp study	Single dose of 0.5 IU/kg of MYL IG SC (Process V) vs. MYL IG SC (Process VI) vs Lantus-US SC at 3 separate visits	1°: demonstrate similarity for total exposure for MYL IG (Process V and VI) vs Lantus-US	T1DM subjects	3 single doses with a washout period of 5-28 days between doses	116 randomized, 113 completed
Phase 3 Studies to Support Efficacy and Safety						
NCT02227862/ MYL-GAI-3001	Efficacy and safety: randomized, open-label, multicenter, parallel group trial	MYL IG SC pre-filled pen vs. Lantus-US SC pre-filled pen	1°: NI in change from BL to 24 weeks in HbA1c	T1DM subjects	Run-in: 6 weeks Randomized period: 52 weeks	558 randomized, 517 completed
NCT02227875/ MYL-GAI-3002	Efficacy and safety: randomized, open-label, multicenter, parallel group trial	MYL IG SC pre-filled pen vs. Lantus-US SC pre-filled pen	1°: NI in change from BL to 24 weeks in HbA1c	T2DM subjects	Randomized period: 24 weeks	560 randomized, 490 completed

Abbreviations: IU, International units; NI, non-inferiority; BL, baseline; SC, subcutaneous; Lantus-US, Lantus approved in the United States; Lantus-EU, Lantus approved in the European Union

5.2. Review Strategy

This review focuses on the efficacy and safety findings from the two Phase 3 clinical trials MYL-GAI-3001 and MYL-GAI-3002.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. MYL-GAI-3001

6.1.1. Study Design

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

Study Objective:

The primary objective was to test whether MYL IG once daily was non-inferior to Lantus once daily when administered in combination with mealtime insulin lispro, based on change in HbA1c from baseline to Week 24.

The secondary objective was to compare MYL IG to Lantus at both 24 weeks and 52 weeks, with respect to:

- Immunogenicity: incidence and change from baseline in the relative levels of anti-drug antibodies (ADA), incidence and change from baseline in the relative levels of anti-host cell protein (anti-HCP) antibodies
- Rate per 30 days of hypoglycemic events
- Occurrence of local reactions, systemic reactions, and other adverse events (AEs)
- Device-related safety assessment
- Change in HbA1c from baseline at other scheduled visits
- Change in FPG from baseline
- Change in basal insulin dose per unit body weight (U/kg) from baseline
- Change in 8-point self-monitored blood glucose (SMBG) profile from baseline
- Proportion of participants with HbA1c < 7% at Week 24.

Trial Design

MYL-GAI-3001 was a Phase 3, multi-center, open-label, randomized, parallel group trial that compared the efficacy, immunogenicity, and safety of MYL IG versus Lantus in patients with T1DM. Following a 4 week screening period, there was a 6 week run-in period during which all patients were titrated on Lantus and were switched from their current prandial insulin to Humalog, followed by randomization to either continuation of Lantus or switching to MYL IG for the 52 week treatment period.

Study Treatment

Following the screening period, all patients entered a 6 week run-in period during which they were titrated on US-approved Lantus, as well as pre-meal Humalog, to ensure good blood glucose control. After the run-in period, subjects were randomized to continue Lantus or to receive MYL IG, administered subcutaneously once daily, for 52 weeks. The treatments were dispensed via a pre-filled disposable pen, which contained 100 units/mL with a 3 mL cartridge. After the run-in period, dose titration was kept to a minimum. Dose titration was managed using a dose titration algorithm based on fasting blood glucose values (see Table 2, below).

Table 2: Algorithm for Insulin Dose Titration

Lowest fasting capillary blood glucose (pre-breakfast) value for 3 days	Adjust basal insulin dose (U per dose) (Lantus® or Mylan's insulin glargine)
>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: Clinical study protocol 3001 trial Appendix II: Suggested guidance for insulin dose titration

Key Inclusion Criteria:

- Patients with T1DM, aged 18 to 65 years old, who also fulfilled the following criteria
  - Initiation of insulin within 6 months of diagnosis of T1DM
  - Treatment with basal-bolus insulin for at least 1 year prior to screening

  - Fasting C-peptide < 0.3 nmol/L at screening
  - Previous treatment with a stable dose of Lantus (+/- 15% variation in dose) for at least 3 months prior to screening
  - HbA1c ≤ 9.5% at screening
  - Body mass index (BMI) between 18.5 to 35 kg/m^2 at screening

Key Exclusion Criteria:

- History of ≥ 2 episodes of severe hypoglycemia within 6 months or history of hypoglycemia unawareness
- History of ≥ 1 episode of ketoacidosis within 6 months
- History of autoimmune disorders other than T1DM, or insufficiently treated thyroid disorder
- Patients with the following secondary complications of diabetes:
  - Active proliferative retinopathy
  - Clinical nephrotic syndrome or diabetic nephropathy (as confirmed by serum creatinine > 1.5 times the upper limit of the reference range
  - History of severe neuropathy or cardiac autonomic neuropathy
  - History of limb amputation due to complications of diabetes, or any vascular procedure 1 year prior to screening
  - History of diabetic foot ulcers 1 year prior to screening
- Uncontrolled hypertension (systolic blood pressure [SBP] ≥160 mmHg or diastolic blood pressure [DBP] ≥100 mmHg)
- Uncontrolled hyperlipidemia (LDL > 160 mg/dL or triglycerides > 500 mg/dL
- Uncontrolled hyperthyroidism
- Impaired hepatic function (AST or ALT > 2 times upper limit of reference range and/or serum bilirubin 1.5 times the upper limit of reference range)
- Patients using insulin pump or any anti-diabetic drugs that affected glycemic control other than insulin within 3 months prior to screening
- Moderate insulin resistance, as defined as requiring insulin ≥ 1.5 U/IU/kg/day

Study Endpoints

The primary efficacy endpoint was the change in HbA1c from baseline to Week 24.

Secondary efficacy endpoints included:

- HbA1c change from baseline at scheduled visits
- Change in FPG from baseline at scheduled visits
- Changes in SMBG levels from baseline at scheduled visits: individual pre-meal, individual post-meal, individual 2-hour excursion after meal, bedtime, overall (average) pre-meal,

overall post-meal, overall excursion, 4-point average (pre-meal + bedtime), and daily average
- Changes in daily insulin dose unit/body weight (mealtime insulin, basal insulin, and total insulin) from baseline at scheduled visit.
- Proportion of subjects reaching the target HbA1c (< 7%)

Safety endpoints included:

- hypoglycemic rate
- antibody specific bindings
- incidence of TEAEs
- incidence of SAEs

Other safety endpoints included changes in vital signs, laboratory measurements, ECGs, and assessment of device safety.

Statistical Analysis Plan

The Statistical Reviewer for this Application was Dr. Anna Kettermann. Please refer to her review for detailed discussion of the analytical methodology and efficacy findings of this trial.

The primary efficacy endpoint, change in HbA1c from baseline to Week 24, was compared between Lantus and MYL IG. Non-inferiority of MYL IG to Lantus was established if the upper-bound of the 95% confidence interval did not exceed 0.4% at Week 24. A repeated measures analysis using a restricted maximum likelihood (REML)-based mixed-effect repeated measure model (MMRM), which included treatment group, visit, treatment-by-visit interaction, region, basal insulin dosing time, and baseline HbA1c as covariates, and was used to produce a 95% confidence interval for the difference between MYL IG and Lantus for the mean change of HbA1c at Week 24. The last observation carried forward (LOCF) method was used as a sensitivity analysis. The Applicant performed the primary analysis on the Intention to Treat (ITT) population, as they defined it.

Protocol Amendments

The protocol was amended three times, with the first amendment occurring prior to the enrollment of patients, and the second and third amendment occurring after the start of the study. The only notable modification to the protocol was the decision to perform the primary analysis on the ITT population, rather than the Per Protocol (PP), in the third amendment. Apart from that, the changes to the study protocol were reviewed, and it was determined that the rest of the protocol modifications were relatively minor and unlikely to have an impact on the

integrity of the trial.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study was performed in compliance with Good Clinical Practice (GCP) standards. The protocol, all amendments, and informed consent documents were reviewed by an Independent Ethics Committee (IEC) or IRB where applicable. The Applicant certified the study was conducted according to the submitted protocol, and consistent with the standards established by the Declaration of Helsinki, International Conference on Harmonization Guideline E6 for GCP and in compliance with all local regulations. Informed consent was obtained prior to study subject participation.

Financial Disclosure

The Applicant submitted a Form FDA 3454 for all covered clinical studies, certifying they have not entered into a financial arrangement with any of the clinical investigators participating in the respective studies that could affect the outcome of the study.

Patient Disposition

The Applicant defined the following populations:

Randomized Population
The Randomized population includes all patients who were enrolled and randomized to study drug. For analyses and displays based on the Randomized population, patients were classified according to their randomized treatment.

Intent-To-Treat Population (ITT)
The Applicant defined the ITT population to include: all randomized patients (including patients who may have received the incorrect treatment, did not complete the study, did not comply with the protocol, or who consumed prohibited medication) who had a Baseline (Randomization visit) and at least 1 post-Baseline primary efficacy value. The patients in the ITT population were analyzed according to the treatment group to which they were assigned.

Per Protocol Population (PP)
The PP population includes:
• Patients who completed the study and had HbA1c measurements in accordance with the protocol;
• Patients who discontinued, but had at least 12 weeks of HbA1c data; and
• Patients with no protocol violations that could impact the primary outcome measure.

All protocol deviations and those that could potentially impact the primary outcome measure were documented separately and signed off prior to the database lock (i.e., before un-blinding the study team). The list of patients with deviations leading to exclusion from the PP population was created, reviewed, and documented prior to database lock. Patients who were excluded from the PP population are provided in a listing, along with the reasons for exclusion.

Safety Population
The Safety population includes patients who received at least 1 dose of study drug. If there was any doubt as to whether or not a patient was treated, they were assumed treated for the purposes of the analysis. For the safety analyses, patients were categorized according to the treatment that they received.

Subject disposition for the 3001 study is summarized in

Table 3. A total of 558 patients were randomized to either treatment, with 280 subjects in the MYL IG arm and 278 subjects in the Lantus arm. All 558 patients randomized received at least one dose of study medication, and were therefore included in the Safety Population. One patient from the Lantus treatment arm did not provide any post-baseline efficacy data and was excluded from the Intention to Treat Population by the Sponsor. Of the subjects who were randomized, a total of 517 subjects (92.7%) completed the 24-week treatment period, with 261 subjects (93.2%) in the MYL IG arm, and 256 subjects (92.1%) in the Lantus arm. There were a total of 26 subjects who discontinued the study prematurely (before or at Week 24), with 11 subjects (3.9%) in the MYL IG arm, and 15 subjects (5.4%) in the Lantus arm. The most common reason for study discontinuation at Week 24 was withdrawal of consent with 10 subjects (4 in the MYL IG arm, 6 in the Lantus group), followed by protocol deviation in 7 subjects (4 in the MYL IG arm, 3 in the Lantus group).

There were 4.3% of subjects in the MYL IG group (n=280), and 5% of subjects in the Lantus group (n=278) with missing data (i.e. subjects that did not have a Week 24 HbA1c measurement). Overall, the amount of missing data in this trial was not very large, and was similar between treatment groups.

Table 3: Patient Disposition Trial 3001

Disposition	MYL IG n (%)	Lantus n (%)	Total n (%)	p-value
Patients randomized	**280**	**278**	**558**	
Patients completed the study	261 (93.2)	256 (92.1)	517 (92.7)	
Patients discontinued the study before or at Week 24	11 (3.9)	15 (5.4)	26 (4.7)	0.411
Reasons for study discontinuation before or at Week 24				
Adverse event	2 (0.7)	3 (1.1)	5 (0.9)	
Lost to follow-up	1 (0.4)	2 (0.7)	3 (0.5)	
Protocol deviation	4 (1.4)	3 (1.1)	7 (1.3)	
Withdrawal of consent	4 (1.4)	6 (2.2)	10 (1.8)	
Other	0	1 (0.4)	1 (0.2)	
Patients discontinued the study through end of study	19 (6.8)	22 (7.9)	41 (7.3)	0.610
Reasons for study discontinuation through end of study				
Adverse event	4 (1.4)	3 (1.1)	7 (1.3)	
Lost to follow-up	1 (0.4)	2 (0.7)	3 (0.5)	
Protocol deviation	7 (2.5)	9 (3.2)	16 (2.9)	
Withdrawal of consent	7 (2.5)	6 (2.2)	13 (2.3)	
Other	0	2 (0.7)	2 (0.4)	

Source: Table 10-1 from Sponsor's clinical study report

Protocol Violations/Deviations

There were a total of 96 subjects (34.3%) in the MYL IG group and 88 subjects (31.7%) in the Lantus group who had a major protocol violation. The most common major protocol deviation was use of a prohibited medication (non-allowed insulin products), which occurred in 32 subjects (11.4%) in the MYL IG group, and 27 subjects (9.7%) in the Lantus group. While there were a greater number of subjects with protocol violations in the MYL IG group, I do not think these violations had an effect on the primary efficacy endpoint as the difference between groups was small.

Demographic Characteristics

The demographic characteristics of subjects in study 3001 are summarized below in Table 4. The majority of subjects were Caucasian (94.6%), with a mean BMI of 26.5 kg/m^2. The mean duration of diabetes was 19.2 years, with a baseline HbA1c of 7.4%, and a fasting plasma

glucose of 165.5 mg/dl. The trial was multinational in design, with the majority of subjects coming from Europe. Treatment arms were balanced in terms of age, gender, race, ethnicity, BMI, and duration of T1DM. The demographic characteristics of study subjects are representative of the population of the US, as well as generally representative of the T1DM population, with the exception of race, as the vast majority of study subjects were Caucasian. However, I do not think the disproportionate number of Caucasian study subjects had any effect on the outcome of the study.

Table 4: Demographic and Baseline Characteristics (Safety Population) Trial 3001

Demographic Parameters	**Lantus N=278**		**MYL-IG N= 280 n (%)**	
Sex				
Male	172	61.9%	164	58.6%
Female	106	38.1%	116	41.4%
Age (years)				
Mean (SD)	42.2	12.0	42.0	12.0
Median	41.0	-	41.0	0
Min, max	19, 65	-	18, 66	-
Age Group				
18-21	5	0.6%	5	0.6%
≥ 22-45 years	161	19.3%	159	19.1%
≥ 46-65 years	112	13.5%	115	13.8%
> 65-75 years	0	0.0%	1	0.1%
Race				
White	265	95.3%	263	93.9%
Black or African American	5	1.8%	2	0.7%
Asian	2	0.7%	2	0.7%
Other	3	1.1%	7	2.5%
Ethnicity				
Hispanic or Latino	3	1.1%	6	2.1%
Not Hispanic or Latino	275	98.9%	274	97.9%
Region				
United States	111	39.9%	116	41.4%
Canada	15	5.4%	10	3.6%
Europe	145	52.2%	145	51.8%
S. Africa	7	2.5%	3	1.1%
Clinical Characteristics				
BMI kg/m^2- mean ± SD	26.6	4.2	26.4	3.7
<25	118	42.5%	103	36.8%
>=25 to <30	92	33.1%	127	45.4%
>=30	68	24.5%	50	17.9%
HbA1c, %- mean ± SD	7.4%	0.8	7.4%	0.9
Duration of diabetes (years) - mean ± SD	19.7	11.3	18.7	11.8
FPG mg/dL mean ± SD	163	61.6	167	68.4

eGFR, mL/min/1.73m^2 — mean ± SD	88.0	16.4	88.5	16.5
30-44 mL/min/1.73m^2 — no. (%)	0	0.0%	1	0.1%
45-59 mL/min/1.73m^2 — no. (%)	10	1.2%	11	1.3%
60-89 mL/min/1.73m^2 — no. (%)	148	17.8%	145	17.4%
≥90 mL/min/1.73m^2 — no. (%)	120	14.4%	123	14.8%
Medical History- Diabetic Complications				
Diabetic Retinopathy	47	16.9%	59	21.1%
Diabetic Nephropathy	10	3.6%	19	6.8%
Diabetic Neuropathy	41	14.8%	53	18.9%

* in years
FPG- Fasting Plasma Glucose

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The majority of patients were compliant with study medications. Three subjects (1.1%) in the MYL IG group missed either mealtime or basal insulin for 5 consecutive days. Rescue medication was not initiated for any patient.

For study results, please see Section 7.1.

6.2. MYL-GAI-3002

6.2.1. Study Design

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 2 Diabetes Mellitus Patients

Study Objective:

The primary objective was to test whether MYL IG once daily was non-inferior to Lantus once daily when administered in combination with oral antidiabetic drugs (OADs), based on change in HbA1c from baseline to Week 24.

The secondary objective was to compare MYL IG to Lantus at Week 24 with respect to:

- Rate of hypoglycemic events per 30 days and hypoglycemia occurrence
- Occurrence of local reactions, systemic reactions, and other adverse events (AEs)
- Immunogenicity: change in titer, incidence and change from baseline in anti-drug antibodies (ADA), anti-host cell protein (anti-HCP) antibodies, and neutralizing antibodies
- Device-related safety assessment
- Change in HbA1c from baseline to Week 12

- Change in FPG from baseline
- Change in basal insulin dose per unit body weight (U/kg) from baseline
- Change in 7-point self-monitored blood glucose (SMBG) profile from baseline
- Proportion of participants with HbA1c < 7% at end of study

Trial Design

MYL-GAI-3002 was a Phase 3, multi-center, open-label, randomized, parallel group trial that compared the efficacy, immunogenicity, and safety of MYL IG versus Lantus in patients with T2DM. During the first 12 weeks of the 24 week treatment period, subjects underwent titration of either MYL IG or Lantus, and during the following 12 weeks, the insulin dose was maintained with minimal titration. The dose of OADs remained unchanged during the study. A total of 560 patients were planned to be enrolled in the study.

Study Treatment

Following a 4 week screening period, subjects were randomized to either US-approved Lantus or MYL IG, administered subcutaneously once daily, for 24 weeks. For the first 12 weeks, the dose of MYL IG or Lantus was titrated. During the second 12 week period, dose titration was kept to a minimum. The treatments were dispensed via a pre-filled disposable pen, which contained 100 units/mL with a 3 mL cartridge. Dose titration was managed using a dose titration algorithm based on fasting blood glucose values (see Table 5, below).

Table 5: Algorithm for Insulin Dose Titration

Lowest fasting capillary blood glucose (pre-breakfast) value for 3 days	Adjust basal insulin dose (U per dose) (Lantus® or Mylan's insulin glargine)
>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: Clinical study protocol trial 3002 Appendix II: Suggested guidance for insulin dose titration

Key Inclusion Criteria:

- Patients with T2DM (per American Diabetes Association 2014 criteria), aged 18 to 65 years old, who also fulfilled the following criteria:
    - Diagnosis of T2DM 1 year prior to screening
    - Confirmatory C-peptide screening
    - Stable dose of OADs at least 3 months prior to screening
    - Insulin naïve OR previous treatment with a stable dose of Lantus (+/- 15% variation in dose) for at least 3 months prior to screening
    - HbA1c ≤ 10.5% at screening or > 7.5 to ≤ 10.5% for insulin naïve patient at screening
    - Body mass index (BMI) between 18.5 to 40 kg/m^2 at screening

Key Exclusion Criteria:

- Requirement of basal-bolus insulin therapy in order to achieve glycemic control
- History of autoimmune disease other than sufficiently treated autoimmune thyroid disorders
- History of ≥ 2 episodes of severe hypoglycemia within 6 months or history of hypoglycemia unawareness
- History of ≥ 1 episode of hyperglycemic hyperosmolar coma or emergency room visit for uncontrolled diabetes leading to hospitalization within 6 months prior to screening
- Patients with the following secondary complications of diabetes:
    - Active proliferative retinopathy
    - Clinical nephrotic syndrome or diabetic nephropathy (as confirmed by serum creatinine > 1.5 times the upper limit of the reference range
    - History of severe neuropathy or cardiac autonomic neuropathy
    - History of limb amputation due to complications of diabetes, or any vascular procedure 1 year prior to screening
    - History of diabetic foot ulcers 1 year prior to screening
- Uncontrolled hypertension (systolic blood pressure [SBP] ≥160 mmHg or diastolic blood pressure [DBP] ≥100 mmHg)
- Uncontrolled hyperlipidemia (LDL > 160 mg/dL or triglycerides > 500 mg/dL
- Uncontrolled hyperthyroidism
- Impaired hepatic function (AST or ALT > 2 times upper limit of reference range and/or serum bilirubin 1.5 times the upper limit of reference range)
- Moderate insulin resistance, as defined as requiring insulin ≥ 1.5 U/IU/kg/day

Study Endpoints

The primary efficacy endpoint was the change in HbA1c from baseline to Week 24.

Secondary efficacy endpoints included:

- HbA1c change from baseline at scheduled visits
- Change in FPG from baseline at scheduled visits
- Changes in SMBG levels from baseline at scheduled visits: individual pre-meal, individual post-meal, individual 2-hour excursion after meal, bedtime, overall (average) pre-meal, overall post-meal, overall excursion, 4-point average (pre-meal + bedtime), and daily average
- Changes in daily insulin dose unit/body weight (mealtime insulin, basal insulin, and total insulin) from baseline at scheduled visit.
- Proportion of subjects reaching the target HbA1c (< 7%)

Safety endpoints included:

- hypoglycemic rate
- antibody specific bindings
- incidence of TEAEs
- incidence of SAEs

Other safety endpoints included changes in vital signs, laboratory measurements, ECGs, and assessment of device safety.

Statistical Analysis Plan

For a detailed discussion of the analytical methodology and efficacy findings of this trial, please refer to Dr. Anna Kettermann's review.

As in the 3001 trial, the primary efficacy endpoint, change in HbA1c from baseline to Week 24, was compared between Lantus and MYL IG. Non-inferiority of MYL IG to Lantus was established if the upper-bound of the 95% confidence interval did not exceed 0.4% at Week 24. A repeated measures analysis using a restricted maximum likelihood (REML)-based mixed-effect repeated measure model (MMRM), which included treatment group, visit, treatment-by-visit interaction, region, basal insulin dosing time, and baseline HbA1c as covariates, and was used to produce a 95% confidence interval for the difference between MYL IG and Lantus for the mean change of HbA1c at Week 24. The last observation carried forward (LOCF) method was used as a sensitivity analysis. The Applicant performed the primary analysis on the Intention to Treat (ITT) population, as they defined it.

Protocol Amendments

As with the 3001 study, the study protocol for the 3002 trial was amended three times. The only notable modification to the protocol was the decision to perform the primary analysis on the ITT population, rather than the Per Protocol (PP), in the third amendment. Apart from that, the changes to the study protocol were reviewed, and it was determined that the rest of the protocol modifications were relatively minor and unlikely to have an impact on the integrity of the trial.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study was performed in compliance with Good Clinical Practice (GCP) standards. The protocol, all amendments, and informed consent documents were reviewed by an Independent Ethics Committee (IEC) or IRB where applicable. The Applicant certified the study was conducted according to the submitted protocol, and consistent with the standards established by the Declaration of Helsinki, International Conference on Harmonization Guideline E6 for GCP and in compliance with all local regulations. Informed consent was obtained prior to study subject participation.

Financial Disclosure

The Applicant submitted a Form FDA 3454 for all covered clinical studies, certifying they have not entered into a financial arrangement with any of the clinical investigators participating in the respective studies that could affect the outcome of the study.

Patient Disposition

Subject disposition is summarized in Table 6. A total of 560 patients were randomized to either treatment, with 277 subjects in the MYL IG arm and 283 subjects in the Lantus arm. Of the 560 patients randomized, 558 patients received at least one dose of study medication, and were therefore included in the Safety Population.

Of the subjects who were randomized, a total of 490 subjects (87.5%) completed the 24-week treatment period, with 240 subjects (86.6%) in the MYL IG arm, and 250 subjects (88.3%) in the Lantus arm. There were a total of 70 subjects who discontinued the study prematurely (before or at Week 24), with 37 subjects (13.4%) in the MYL IG arm, and 33 subjects (11.7%) in the Lantus arm. The most common reason for study discontinuation at Week 24 was withdrawal of

consent with 25 subjects (12 in the MYL IG arm, 13 in the Lantus group), followed by protocol deviation in 17 subjects (10 in the MYL IG arm, 7 in the Lantus group).

Per the Applicant, eight patients did not provide either baseline or post-baseline efficacy data and were excluded from the Applicant defined ITT Population. As in the 3001 study, the Applicant's definition of Intention to Treat included any randomized patient who had a baseline and at least 1 post-baseline primary efficacy value. The ITT population was used for all efficacy analyses, and the Safety Population was used for the safety analysis.

There were 11.6% of subjects in the MYL IG group (n=277), and 11.3% of subjects in the Lantus group (n=283) with missing data (i.e. subjects that did not have a Week 24 HbA1c measurement). Please refer to Anna Kettermann's review for methods to address missing data in the efficacy analyses.

Reviewer comment: FDA defines the ITT population as all the subjects who undergo randomization. The FDA statistical review relies on the standard FDA definition of ITT for the primary efficacy analysis.

Table 6: Patient Disposition Trial 3002

	MYL IG (N=277)	Lantus (N=283)	Total (N=560)	
Disposition	**n (%)**	**n (%)**	**n (%)**	**p-value**
Patients completed study	240 (86.6)	250 (88.3)	490 (87.5)	
Patients discontinued study	37 (13.4)	33 (11.7)	70 (12.5)	0.544
Reason for study discontinuation				
Withdrawal of consent	12 (4.3)	13 (4.6)	25 (4.5)	
Protocol violation	10 (3.6)	7 (2.5)	17 (3.0)	
Adverse event	3 (1.1)	0	3 (0.5)	
Lost to follow-up	10 (3.6)	10 (3.5)	20 (3.6)	
The Investigator or the sponsor, for any reason, terminates the study prematurely[1]	1 (0.4)	0	1 (0.2)	
Other	1 (0.4)	3 (1.1)	4 (0.7)	

Source: Table 10-1 from the Sponsor's Clinical Study Report

Protocol Violations/Deviations

There were a total of 67 subjects (24.2%) in the MYL IG group and 84 subjects (29.7%) in the Lantus group who had a major protocol violation. The most common major protocol deviation was use of a prohibited medication (non-allowed insulins and new non-insulin

antihyperglycemic agents), which occurred in 29 subjects (10.5%) in the MYL IG group, and 41 subjects (14.5%) in the Lantus group. There were a greater number of subjects with protocol violations in the Lantus group, and as with the 3001 trial, I do not think these violations had an effect on the primary efficacy endpoint as the difference between groups was small.

Table of Demographic Characteristics

The demographic characteristics of subjects in study 3002 are summarized below in Table 7. The majority of subjects were Caucasian (52.7%), although a significant proportion of subjects were Hispanic (26.6%), with a mean BMI of 31.5 kg/m^2. The mean duration of diabetes was 11.6 years, with a baseline HbA1c of 8.1%, and a fasting plasma glucose of 154.8 mg/dl. The trial was conducted internationally, although a significant majority of subjects were from the United States. Treatment arms were generally balanced in terms of age, gender, BMI, and duration of T2DM. While there was a nominally statistically significant difference in race (p=0.01) between groups, this difference is unlikely to have impacted the results.

Table 7: Demographic and Baseline Characteristics (Randomized Population) Trial 3002

Demographic Parameters	Lantus N=283		MYL-IG N= 277 n (%)	
Sex				
Male	165	58.3%	147	53.1%
Female	118	41.7%	130	46.9%
Age (years)				
Mean (SD)	55.2	7.5	55.0	7.9
Median	56	-	57	-
Min, max	29, 65	-	25, 65	-
Age Group				
22-45 years	34	12.0	36	13.0
≥ 46-65 years	249	88.0	241	87.0
Race				
White	148	52.3%	147	53.1%
Black or African American	18	6.4%	37	13.4%
Asian	19	6.7%	9	3.2%
Native Hawaiian or other Pacific Islander	4	1.4%	0	0.0%
American Indian or Alaska Native	1	0.4%	0	0.0%
Other	17	6.0%	11	4.0%
Ethnicity				
Hispanic or Latino	76	26.9%	73	26.4%
Not Hispanic or Latino	207	73.1%	204	73.6%
Region				
United States	228	80.6%	225	81.2%

Asia	4	1.4%	4	1.4%
Europe	33	11.7%	34	12.3%
Middle East and Africa	18	6.4%	14	5.1%
Clinical Characteristics				
BMI kg/m^2- mean ± SD	31.5	4.4	31.6	4.8
<25	18	6.4%	25	9.0%
>=25 to <30	93	32.9%	80	28.9%
>=30	171	60.4%	171	61.7%
HbA1c, %- mean ± SD	8.1%	1.1	8.1%	1.1
Duration of (years) — mean ± SD	11.4	6.0	12.0	7.1
Fasting Plasma Glucose mg/dL	154.8	55.8	154.8	54.0
eGFR, mL/min/1.73m^2 — mean ± SD	87.2	21.5	86.6	19.9
30-44 mL/min/1.73m^2 — no. (%)	2	0.7%	1	0.4%
45-59 mL/min/1.73m^2 — no. (%)	21	7.5%	24	8.7%
60-89 mL/min/1.73m^2 — no. (%)	148	52.5%	137	49.6%
≥90 mL/min/1.73m^2 — no. (%)	111	39.4%	114	41.3%
Medical History- Diabetic Complications				
Diabetic Retinopathy	23	8.2%	23	8.3%
Diabetic Nephropathy	11	3.9%	10	3.6%
Diabetic Neuropathy	38	13.5%	49	17.8%

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The majority of patients were compliant with the study drug, with only 3 subjects (1.1%) in the MYL IG group and 8 subjects (2.8%) in the Lantus group missing either mealtime or basal insulin doses for 5 or more consecutive days, and 2 subjects (0.7%) in each group missing either mealtime or basal insulin for 30 cumulative days for a patient who completed the study, or >20% of treatment days for a patient who prematurely discontinued. None of the patients required the use of rescue medication during the trial.

For study results, please see Section 7.1.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

For both trials, the primary efficacy endpoint was change in HbA1c from baseline to Week 24. The Applicant performed the efficacy analyses on their defined ITT population. The Applicant performed a repeated measures analysis using a restricted maximum likelihood (REML)-based mixed-effect repeated measure model (MMRM). The MMRM model was used to produce a 95% confidence interval for the difference between MYL IG and Lantus for the mean change of HbA1c at Week 24. The Agency reanalyzed the data using a Return to baseline multiple imputation analysis, which is considered the Agency's preferred method for handling missing data. For further details, please see Dr. Anna Kettermann's Statistical review. The results are presented in Table 8 below.

Using the Return to baseline analysis, for study 3001, at Week 24, the change in HbA1c was 0.11 (0.05 to 0.18) for MYL IG, and 0.08 (0.02 to 0.15) for Lantus. The mean difference between groups was 0.03 (-0.06 to 0.12). For study 3002, the change in HbA1c at Week 24 was -0.37 (-0.49 to -0.26) for MYL IG, and -0.42 (-0.54 to -0.31) for Lantus. The mean difference between groups was 0.05 (-0.11 to 0.21). Overall, for both trials 3001 and 3002, MYL IG was non-inferior to Lantus using either MMRM or Return to baseline analyses.

During the course of the review, it was found that the Applicant inappropriately excluded several patients from the ITT population for lacking post-baseline efficacy data. However, the small number of patients (n=1 for the 3001 trial and n=8 for the 3002 trial) excluded are unlikely to change the efficacy results significantly, so the Applicant's analyses will be presented here. However, as it is the FDA's preferred methodology for analyzing the primary endpoint and for handling missing data, and for the purposes of labeling, for all results presenting change in HbA1c, the FDA Statistical reviewer recommends using outcomes based on analysis involving multiple imputations. I agree with Dr. Kettermann's concerns with the Applicant's analyses, and I relied on the results presented in her review to inform the conclusions of my clinical review.

Table 8: Primary Efficacy Analysis Mean Change in HbA1c (Trials 3001 and 3002)

Study Analytical Approach	Treatment Arm	Number of Subjects	Mean Baseline HbA1c (%)	LS Mean HbA1c Change from Baseline (95% CI)	LS Mean Treatment Difference: MYL IG vs. Lantus (95% CI)
3001 (T1DM)					
MMRM*	MYL IG	280	7.37	0.14 (0.03, 0.24)	0.03 (-0.66, 0.12)
	Lantus	277	7.39	0.11 (0.01, 0.22)	
Return to baseline ¶	MYL IG	280		0.11 (0.05, 0.18)	0.03 (-0.06, 0.12)
	Lantus	278		0.08 (0.02, 0.15)	
3002 (T2DM)					
MMRM*	MYL IG	274	8.14	-0.60 (-0.78, -0.41)	0.06 (-0.10, 0.22)

	Lantus	278	8.00	-0.66 (-0.84, -0.48)	
Return to baseline ¶	MYL IG	277		-0.37 (-0.49, -0.26)	0.05 (-0.11, 0.21)
	Lantus	283		-0.42 (-0.54, -0.31)	

Abbreviations: CI, confidence interval; MMRM, mixed-effect repeated measures model; HbA1c, hemoglobin A1c; LS, least squares; T1DM, type 1 diabetes; T2DM, type 2 diabetes; and vs, versus.
*Applicant's analysis of the primary efficacy endpoint. Note the number of subjects differs as in the Applicant's analysis, patients in the ITT population were excluded if they lacked post-baseline efficacy data
¶ Agency's reanalysis of the primary efficacy endpoint. This analysis includes subjects who were excluded from the Applicant's analysis.

The Applicant performed additional analyses using the MMRM model for the change in HbA1c from baseline to Week 52 between treatment groups for study 3001. The mean difference between groups was -0.05 (-0.15, 0.06), and the upper bound of the 95% CI (0.06) was also less than the non-inferiority margin of 0.4.

7.1.2. Secondary and Other Endpoints

The Applicant analyzed mean changes in FPG from baseline to Weeks 12, 24, 36, and 52. For the 3001 trial, at Week 24, the mean change from baseline (in mg/dL) for MYL IG was -14.6, and for Lantus it was 1.6. This was a statistically significant difference between the treatment groups (p= 0.017), with the 95% CI for the difference of -24.6 to -2.4. At all other time points (Weeks 12, 36, and 52), there was no significant difference between the groups. For study 3002, at Week 24, the mean change from baseline (in mg/dL) for MYL IG was -13.3, and for Lantus it was -18.9. The difference between groups was not statistically significant (p= 0.071), with the 95% CI for the difference of -0.5 to 13.1. There was no significant difference between treatment groups at any other time points.

The proportion of subjects achieving a HbA1c of <7% at Week 24 were similar between MYL IG-treated subjects versus Lantus-treated subjects in both the 3001 study (23.2% [65/280 subjects] vs. 22.0% [61/277 subjects], respectively) and the 3002 study (23.0% [63/274 subjects] vs. 24.5% [68/278 subjects], respectively).

7.1.3. Subpopulations

Dr. Anna Kettermann performed additional subgroup analyses for the primary efficacy endpoint using sex (females, males), race (Caucasian, Black, and Hispanic), age (< 65 years; ≥ 65 years), geographic region (Europe, Eastern Europe, Middle East, and North America), and baseline HbA1c (<7.5%; ≥ 7.5%) in her Statistical Review. Of note, the majority of subjects with T1DM in the 3001 study were Caucasian, which is reflective of the disease population, and most of the subjects in both trials were younger than 65 years old. The subgroup analyses did not reveal

any evidence of a treatment difference in the different subgroups. With respect to baseline HbA1c, Dr. Kettermann's findings suggest that the effect of MYL IG on HbA1c was similar in each study and in each HbA1c subgroup.

7.1.4. Dose and Dose-Response

Since efficacy outcomes depend on optimal insulin dose titration, the average daily basal insulin dose, the average prandial insulin dose (for the 3001 trial), as well as the change from baseline in insulin doses were reviewed. For the 3001 trial, the baseline average daily basal dose was lower in the MYL IG group compared to the Lantus group, but by Week 12, the MYL IG group had a greater increase in basal daily dose compared to the Lantus group. The differences in the mean change from baseline between groups were nominally statistically significant starting at Week 2 (data not shown) through Week 24. However, while the differences in mean change from baseline between groups were significant, I do not consider the difference in change from baseline between group differences to be clinically relevant, as the MYL IG group started with a lower baseline daily basal insulin dose, and despite the increase in MYL IG group dose, the actual insulin dose values were similar between MYL IG and Lantus. There were also no statistically significant differences between the treatment groups in change from baseline in prandial insulin dose. For the 3002 trial, both the MYL IG and Lantus groups had statistically significant increases from baseline in the daily basal insulin dose, however, there were no significant differences between groups at any time point. The daily basal insulin dose results are presented in Table 9, below, and graphically, in Figure 1 and

Figure 2. Overall, the data does not demonstrate a difference in insulin dose for the MYL IG versus Lantus groups to suggest a clinically relevant difference in potency.

Table 9: Mean Daily Basal Insulin Doses (Trials 3001 and 3002)

Study Basal Insulin Dosing	Treatment Arm	Number of Subjects	Basal Insulin Dose U/kg (SD)	Mean Change from Baseline (SD)	LS Mean Treatment Difference: MYL IG vs. Lantus (95% CI)
3001 (T1DM)					
Baseline	MYL IG	278	0.31 (0.12)	-	-
	Lantus	275	0.33 (0.15)	-	-
Week 12	MYL IG	271	0.32 (0.12)	0.0096 (0.0349)	0.004 (0.003, 0.014)
	Lantus	265	0.33 (0.15)	0.0006 (0.0336)	-
Week 24	MYL IG	267	0.33 (0.13)	0.0152 (0.0453)	0.002 (0.004, 0.019)
	Lantus	262	0.33 (0.15)	0.0039 (0.0410)	-
Week 36	MYL IG	264	0.33 (0.13)	0.0141 (0.0427)	0.016 (0.002, 0.017)
	Lantus	254	0.33 (0.16)	0.0047 (0.0485)	-

Week 52	MYL IG	265	0.33 (0.12)	0.0128 (0.0481)	0.053 (0.000, 0.016)
	Lantus	261	0.33 (0.15)	0.0043 (0.0482)	
3002 (T2DM)					
Baseline	MYL IG	249	0.22 (0.25)	-	0.06 (-0.10, 0.22)
	Lantus	259	0.24 (0.28)	-	-
Week 12	MYL IG	251	0.35 (0.21)	0.1062 (0.1198)	0.58 (-0.02, 0.01)
	Lantus	257	0.36 (0.23)	0.1065 (0.1301)	-
Week 24	MYL IG	250	0.36 (0.21)	0.1244 (0.1386)	0.757 (-0.022, 0.016)
	Lantus	252	0.38 (0.23)	0.1220 (0.1418)	-

Source: created using JReview and ADSL.XPT and EXP.XPT datasets for trials 3001 and 3002.

Figure 1: Mean Daily Basal Insulin Doses (U/kg) (Trial 3001)

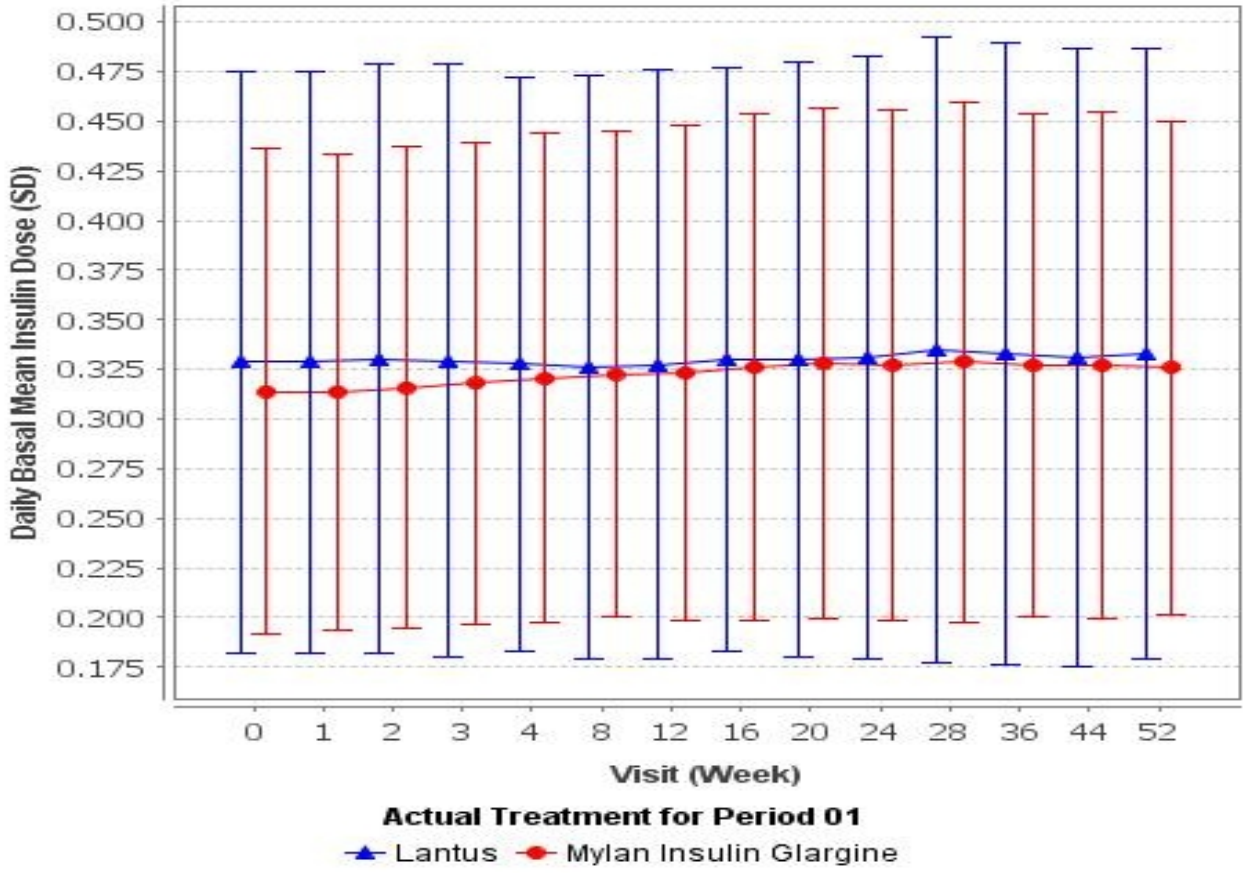
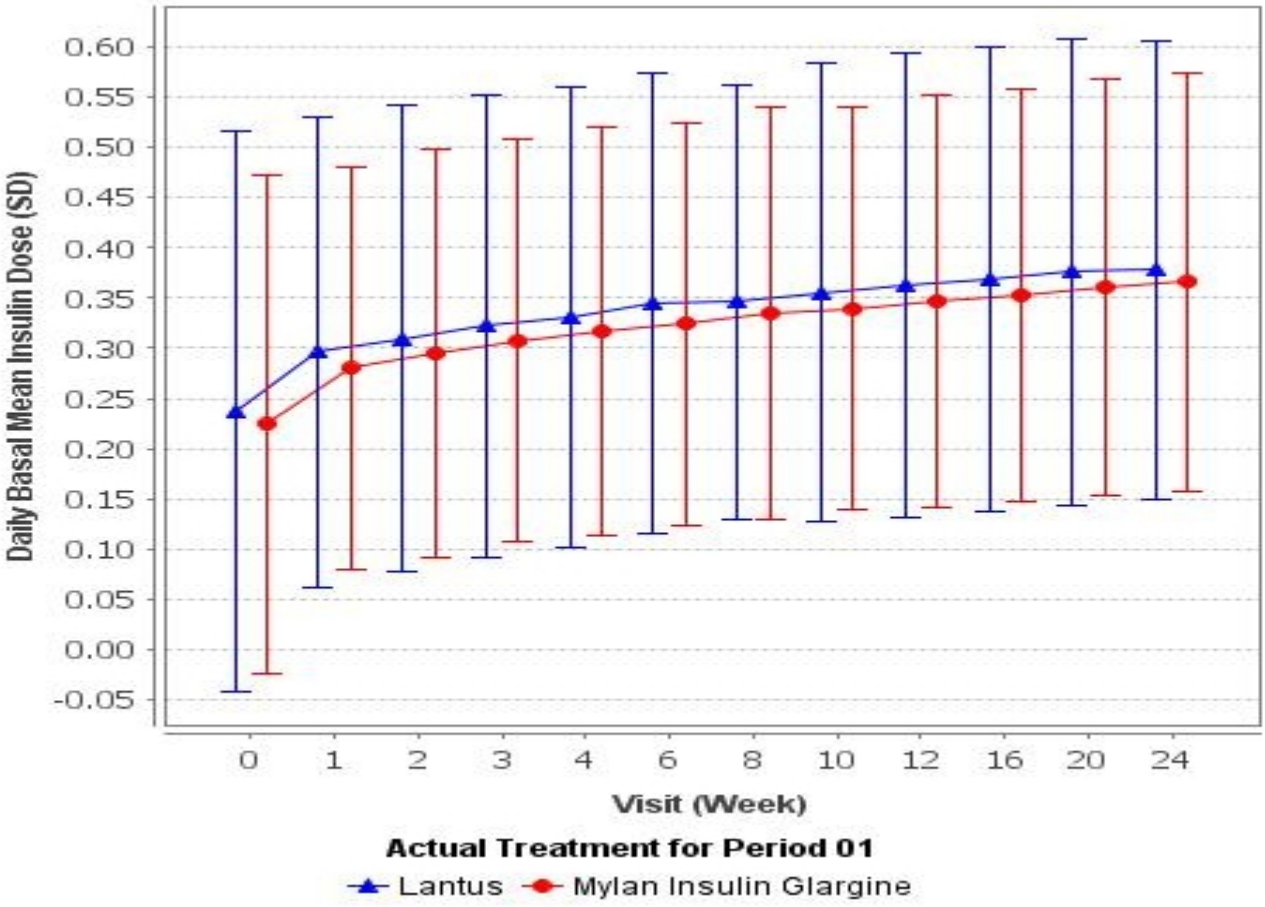


Figure 2: Mean Daily Basal Insulin Doses (U/kg) (Trial 3002)

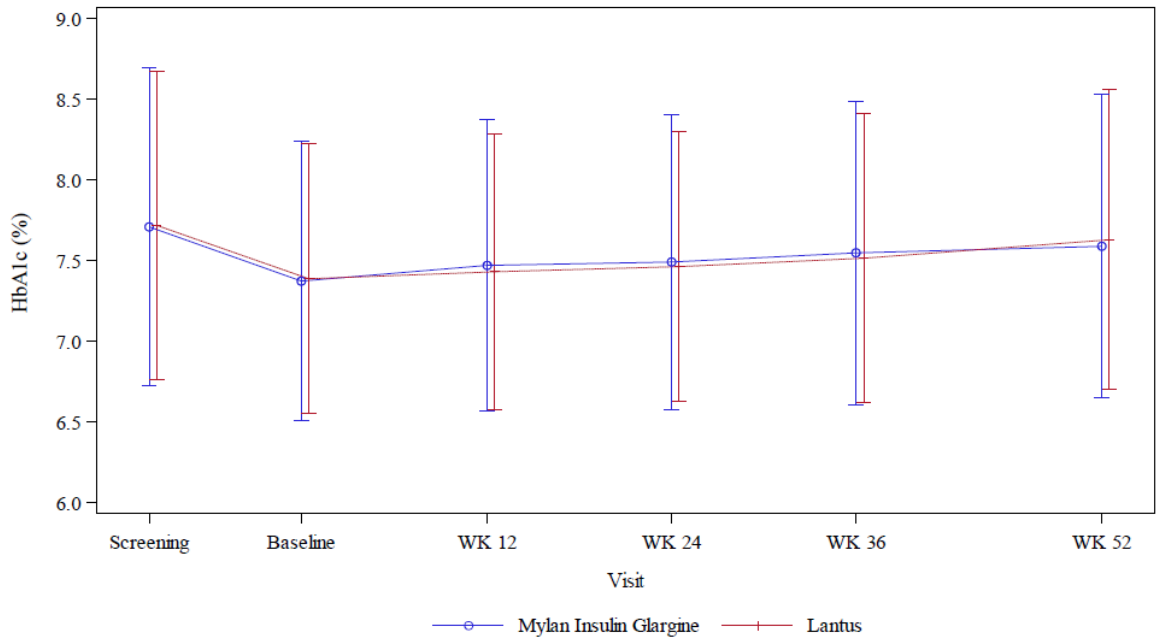


Source: created using JReview and ADSL.XPT and EXP.XPT datasets for trials 3001 and 3002.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

In the 3001 trial, the primary efficacy endpoint of change in HbA1c was collected after a 24 week treatment period, however, the full treatment period was extended out to 52 weeks in order to obtain long-term safety and immunogenicity data and was a secondary efficacy endpoint. As seen in the Figure 3, below, there was a decrease in HbA1c in both groups from screening to baseline values, followed by a small but statistically significant increase in both groups starting at Week 12, and continuing through Week 52. There was no difference between the two treatment groups at any time point. Although there was a trend toward increasing HbA1c throughout the trial, the data demonstrate the durability of the glycemic effect of MYL IG.

Figure 3: HbA1c over Time (Trial 3001)



Source: Sponsor's Clinical Study Report Figure 11-1

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The insulin glargine product studied in the phase 3 clinical trials was manufactured using Process V at a facility in India, while the to-be marketed product is manufactured using Process VI at a facility in Malaysia. It is not clear whether differences in impurities and immunogenicity will impact the efficacy and safety of the to-be marketed drug product. This issue is further discussed in 4.2.

7.2.2. Other Relevant Benefits

The Applicant has not proposed nor established a benefit to patients of MYL IG over Lantus or other currently available long acting insulin products.

7.3. Integrated Assessment of Effectiveness

The effectiveness of Process V MYL IG in addition to prandial insulin in patients with T1DM, as

well as in addition to antihyperglycemic medications in patients with T2DM, was evaluated in two trials (Trials 3001 and 3002 respectively). The primary endpoint for both trials was change in HbA1c from baseline to Week 24. While there were differences in mean change from baseline between groups, the actual insulin dose values were similar, and the data overall demonstrates that Process V MYL IG was non-inferior to Lantus with respect to the primary endpoint of change from baseline to Week 24 of HbA1c. However, the Applicant has proposed marketing MYL IG generated from Process VI. The Applicant has not provided an adequate clinical bridge to support the use of data from trials using Process V MYL IG to make a determination about the effectiveness of MYL IG generated by Process VI.

8. Review of Safety

8.1. Safety Review Approach

The safety analysis was limited to the two Phase 3 trials, MYL-GAI-3001 in T1DM subjects, and MYL-GAI-3002 in T2DM subjects.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The overall exposure to MYL IG was in accordance with the recommendations made by the FDA at the End of Phase 2 meeting, in which it was recommended that at least 500 patients with T1DM and 560 patients with T2DM be enrolled in the phase 3 trials. In the 3001 study, there were 280 patients with T1DM with a mean (SD) duration of exposure to MYL IG of 351.0 days (±60.07). In the 3002 trial, there were 276 patients with T2DM with a mean (SD) duration of exposure to MYL IG of 157.3 days (±38.92). Overall, the safety exposure to MYL IG was adequate in terms of the number of subjects exposed to study drug, and in terms of the duration of exposure to support the safety analysis of the application.

8.2.2. Relevant characteristics of the safety population:

For a detailed discussion of the demographic and other baseline disease characteristics of the safety population for both trials 3001 and 3002, please refer to Sections 6.1.2 and 6.2.2, respectively.

8.2.3. Adequacy of the safety database:

The safety database appears sufficiently representative of the disease population and is considered adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The submission quality was considered adequate for review. There were no significant issues regarding data integrity.

8.3.2. Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence, including any new, clinically important abnormal laboratory findings, symptom, or disease, temporally associated with drug administration in a patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. This definition also includes the exacerbation of pre-existing diseases or conditions. The Sponsor categorized a treatment-emergent adverse event (TEAE) if the first onset (or worsening, in the case of pre-existing condition) is after the first administration of MYL IG or Lantus after randomization through follow-up visit or 28 days after the last dose. These events were categorized using Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1.

8.3.3. Routine Clinical Tests

The routine clinical testing included as part of the safety assessment is discussed in section 6 of this review.

8.4. Safety Results

8.4.1. Deaths

There were 3 deaths reported in the 3001 study, which included 1 in the Lantus arm and 2 in the MYL IG arm. The first death associated with MYL IG was attributed to hypoglycemia, and the second cause of death was unknown, although it may have also been related to hypoglycemia. A brief narrative summary of the two deaths associated with MYL IG are below:

- Subject (b) (6): A 42 year old Caucasian male with a medical history that included T1DM, hypertension, essential tremor, back pain, and microalbuminuria was randomized to MYL IG treatment arm. Prior episodes of hypoglycemia were noted during the study, which included eight daytime episodes during the six weeks prior to the fatal hypoglycemic event. The dose of MYL IG was reduced to

23 units during this period, although the patient continued to have hypoglycemic episodes. At his last study visit, the patient's dose of MYL IG was increased from 23 units to 24 units due to elevated fasting blood glucose levels over 200 mg/dl. The patient died approximately 4-5 days after the last study visit, and based on post-mortem vitreous humor glucose value of 16 mg/dL, the cause of death was determined to be due to hypoglycemia.

- Subject (b) (6): A 65 year old Caucasian female with a past medical history which included T1DM, retinopathy, peripheral neuropathy, hypertension, hypothyroidism, and renal failure was randomized to the MYL IG treatment arm. Almost a year after starting treatment in the study, the patient was found dead in bed. The cause of death was undetermined.

The first death is attributable to hypoglycemia, while the cause of death in the second case is unknown, although hypoglycemia may have potentially contributed. Hypoglycemia is an unfortunate but not unexpected side effect of insulin use. Overall, I do not find the small number of deaths in this study to be concerning.

There were no deaths reported in study 3002.

8.4.2. Serious Adverse Events

There were a total of 40 SAEs in the 3001 trial, which occurred in 22 subjects (7.9%) in the Lantus arm and 18 subjects (6.4%) in the MYL IG arm. There were no significant differences in the overall incidence of SAEs between treatment groups. The highest number of reported SAEs occurred in the "Metabolism and nutrition disorders" SOC, which included 7 events of hypoglycemia in the MYL IG arm and 10 in the Lantus arm. The SOC of "Nervous system disorders" also had 2 events in the MYL IG arm related to hypoglycemia, reported as epilepsy and hypoglycemic seizure, compared to 2 reported events of generalized tonic-clonic seizure in the Lantus arm.

There was one report of a SAE of death reported in the MYL IG arm. This event is discussed further in Section 8.4.1.

Table 10: Summary of Serious Adverse Events- Trial 3001

System Organ Class Dictionary Derived Term	Lantus n=278		Mylan IG n=280		Total n=558	
METABOLISM AND NUTRITION DISORDERS	10	3.6%	7	2.5%	17	2.0%
HYPOGLYCAEMIA	10	3.6%	7	2.5%	17	2.0%

INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3	1.1%	2	0.7%	5	0.6%
FEMORAL NECK FRACTURE	0	0.0%	1	0.4%	1	0.1%
FEMUR FRACTURE	1	0.4%	0	0.0%	1	0.1%
LOWER LIMB FRACTURE	1	0.4%	0	0.0%	1	0.1%
POSTOPERATIVE RESPIRATORY DISTRESS	0	0.0%	1	0.4%	1	0.1%
SCAPULA FRACTURE	1	0.4%	0	0.0%	1	0.1%
UPPER LIMB FRACTURE	1	0.4%	0	0.0%	1	0.1%
NERVOUS SYSTEM DISORDERS	3	1.1%	2	0.7%	5	0.6%
EPILEPSY	0	0.0%	1	0.4%	1	0.1%
GENERALISED TONIC-CLONIC SEIZURE	2	0.7%	0	0.0%	2	0.2%
HYPOGLYCAEMIC SEIZURE	0	0.0%	1	0.4%	1	0.1%
ISCHAEMIC STROKE	1	0.4%	0	0.0%	1	0.1%
INFECTIONS AND INFESTATIONS	2	0.7%	2	0.7%	4	0.5%
CELLULITIS	1	0.4%	0	0.0%	1	0.1%
DIVERTICULITIS	0	0.0%	1	0.4%	1	0.1%
HAEMATOMA INFECTION	1	0.4%	0	0.0%	1	0.1%
PHARYNGITIS	0	0.0%	1	0.4%	1	0.1%
PNEUMONIA	1	0.4%	0	0.0%	1	0.1%
PYELONEPHRITIS ACUTE	0	0.0%	1	0.4%	1	0.1%
UROSEPSIS	0	0.0%	1	0.4%	1	0.1%
VIRAL RASH	1	0.4%	0	0.0%	1	0.1%
CARDIAC DISORDERS	2	0.7%	2	0.7%	4	0.5%
ATRIAL FIBRILLATION	0	0.0%	1	0.4%	1	0.1%
CORONARY ARTERY DISEASE	1	0.4%	1	0.4%	2	0.2%
MYOCARDIAL INFARCTION	1	0.4%	0	0.0%	1	0.1%
RENAL AND URINARY DISORDERS	0	0.0%	3	1.1%	3	0.4%
ACUTE KIDNEY INJURY	0	0.0%	2	0.7%	2	0.2%
GLOMERULONEPHRITIS MINIMAL LESION	0	0.0%	1	0.4%	1	0.1%
ENDOCRINE DISORDERS	3	1.1%	0	0.0%	3	0.4%
GOITRE	2	0.7%	0	0.0%	2	0.2%
HYPOTHYROIDISM	1	0.4%	0	0.0%	1	0.1%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	0.4%	1	0.4%	2	0.2%
CERVICAL SPINAL STENOSIS	1	0.4%	0	0.0%	1	0.1%
OSTEOCHONDROSIS	0	0.0%	1	0.4%	1	0.1%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0.0%	1	0.4%	1	0.1%
PLEURAL EFFUSION	0	0.0%	1	0.4%	1	0.1%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	0.0%	1	0.4%	1	0.1%
DEATH	0	0.0%	1	0.4%	1	0.1%
EYE DISORDERS	0	0.0%	1	0.4%	1	0.1%
RETINAL ARTERY OCCLUSION	0	0.0%	1	0.4%	1	0.1%

SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	0.0%	1	0.4%	1	0.1%
SKIN ULCER	0	0.0%	1	0.4%	1	0.1%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1	0.4%	0	0.0%	1	0.1%
MALIGNANT OLIGODENDROGLIOMA	1	0.4%	0	0.0%	1	0.1%
PSYCHIATRIC DISORDERS	1	0.4%	0	0.0%	1	0.1%
DEPRESSION	1	0.4%	0	0.0%	1	0.1%
PSYCHOTIC DISORDER	1	0.4%	0	0.0%	1	0.1%
VASCULAR DISORDERS	1	0.4%	0	0.0%	1	0.1%
HYPERTENSION	1	0.4%	0	0.0%	1	0.1%
SUBJECTS WITH ANY SAE	22	7.9%	18	6.4%	40	7.2%

Source: created using JReview and ADSL.XPT and AE.XPT datasets for trial 3001.

There were a total of 17 SAEs in the 3002 trial, which occurred in 9 subjects (3.2%) in the Lantus arm and 8 subjects (2.9%) in the MYL IG arm. There were no significant differences in the overall incidence of SAEs between treatment groups. The highest number of reported SAEs occurred in the "Gastrointestinal disorders" SOC, which included 2 events of pancreatitis in the MYL IG arm. There were no deaths reported in the 3002 trial. Overall, there were a small number of SAEs, with no major imbalances between treatment arms, and those SAEs that occurred are common in the T2DM population.

Table 11: Summary of Serious Adverse Events in Trial 3002 (Safety Population)

System Organ Class Dictionary Derived Term	**Lantus n=282**		**Mylan IG n=276**		**Total n=558**	
GASTROINTESTINAL DISORDERS	**0**	**0**	**3**	**1.1%**	**3**	**0.3%**
GASTRIC ULCER	0	0.0%	1	0.4%	1	0.1%
PANCREATITIS	0	0.0%	1	0.4%	1	0.1%
PANCREATITIS ACUTE	0	0.0%	1	0.4%	1	0.1%
INVESTIGATIONS	**0**	**0.0%**	**2**	**0.7%**	**2**	**0.2%**
HELICOBACTER TEST POSITIVE	0	0.0%	1	0.4%	1	0.1%
HEPATIC ENZYME INCREASED	0	0.0%	1	0.4%	1	0.1%
INFECTIONS AND INFESTATIONS	**2**	**0.7%**	**2**	**0.7%**	**4**	**0.4%**
BRONCHITIS	1	0.4%	1	0.4%	2	0 2%
MENINGITIS VIRAL	1	0.4%	0	0.0%	1	0.1%
PARASPINAL ABSCESS	0	0.0%	1	0.4%	1	0.1%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**0**	**0.0%**	**1**	**0.4%**	**1**	**0.1%**
NON-CARDIAC CHEST PAIN	0	0.0%	1	0.4%	1	0.1%
EYE DISORDERS	**0**	**0.0%**	**1**	**0.4%**	**1**	**0.1%**

EYE HAEMORRHAGE	0	0.0%	1	0.4%	1	0.1%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**0**	**0.0%**	**1**	**0.4%**	**1**	**0.1%**
CERVICAL SPINAL STENOSIS	0	0.0%	1	0.4%	1	0.1%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**1**	**0.4%**	**1**	**0.4%**	**2**	**0.2%**
ASTHMA	0	0.0%	1	0.4%	1	0.1%
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	1	0.4%	0	0.0%	1	0.1%
HYPOXIA	0	0.0%	1	0.4%	1	0.1%
NERVOUS SYSTEM DISORDERS	**1**	**0.4%**	**0**	**0.0%**	**1**	**0.1%**
CEREBROVASCULAR ACCIDENT	1	0.4%	0	0.0%	1	0.1%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**2**	**0.7%**	**0**	**0.0%**	**2**	**0.2%**
ENDOMETRIAL ADENOCARCINOMA	1	0.4%	0	0.0%	1	0.1%
SQUAMOUS CELL CARCINOMA OF SKIN	1	0.4%	0	0.0%	1	0.1%
RENAL AND URINARY DISORDERS	**2**	**0.7%**	**0**	**0.0%**	**2**	**0.2%**
ACUTE KIDNEY INJURY	2	0.7%	0	0.0%	2	0 2%
METABOLISM AND NUTRITION DISORDERS	**3**	**1.1%**	**0**	**0.0%**	**3**	**0.3%**
DEHYDRATION	1	0.4%	0	0.0%	1	0.1%
HYPEROSMOLAR HYPERGLYCAEMIC STATE	1	0.4%	0	0.0%	1	0.1%
HYPOGLYCAEMIA	1	0.4%	0	0.0%	1	0.1%
LACTIC ACIDOSIS	1	0.4%	0	0.0%	1	0.1%
SUBJECTS WITH ANY SAE	**9**	**3.2%**	**8**	**2.9%**	**17**	**3.0%**

Source: created using JReview and ADSL.XPT and AE.XPT datasets for trial 3002.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

During the 24 week treatment period in Trial 3001, there were 2 subjects (0.7%) in the MYL IG group versus 3 subjects (1.1%) in the Lantus group who discontinued the study due to an AE, while a total of 4 subjects (1.4%) in the MYL IG group and 3 (1.1%) subjects in the Lantus group discontinued before Week 52. During the 3002 trial, there were 3 subjects (1.1%) in the MYL IG group versus no subjects in the Lantus group who discontinued the study due to an AE. The reported AEs included asthma, headache, dyspepsia, and depression, and none of the reported AEs leading to dropout were categorized as SAEs. Overall, review of these AEs leading to study

discontinuation does not suggest a concerning safety signal for MYL IG.

8.4.4. Significant Adverse Events

The use of insulin is associated with the risk of hypoglycemia, which can be a serious, life-threatening event. Hypoglycemia can limit effective glycemic management in patients with both T1DM and T2DM.

The Sponsor classified hypoglycemic events using the following definitions:

Severe Hypoglycemia
An event is considered as severe hypoglycemia if it requires the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions which results in neurological recovery, regardless of the availability of a blood glucose measurement. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of normal plasma glucose is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Documented Symptomatic Hypoglycemia
An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).

Asymptomatic Hypoglycemia
An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).

Probable Symptomatic Hypoglycemia.
Characteristic symptoms of hypoglycemia with no blood glucose level measurement that resolved with food intake, subcutaneous glucagon, or intravenous glucose.

Relative Hypoglycemia.
An event during which the patient reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration > 70 mg/dL (3.9 mmol/L).

Nocturnal Hypoglycemia.
Nocturnal hypoglycemia will include hypoglycemia that occurs from the time the patient goes to bed at night till the time he or she wakes up. This may include any of the above 5 types of hypoglycemia.

My review focused on severe hypoglycemia, which is the most clinically serious event. For both studies 3001 and 3002, I reviewed the overall incidence of severe hypoglycemia, focusing on any potential differences between treatment groups, as well as the number of severe hypoglycemia events, as well as the time to first occurrence of a severe hypoglycemic event.

For study 3001, there were 273 subjects (97.5%) that reported any hypoglycemic event in the MYL IG treatment arm, and 269 subjects (96.8%) in the Lantus arm. There were 11 subjects (3.9%) that reported an event of severe hypoglycemia in the MYL IG treatment arm, and 13 subjects (4.7%) in the Lantus arm. Of the subjects that reported an event of severe hypoglycemia, there were 14 episodes of severe hypoglycemia in the MYL IG arm, and 20 episodes in the Lantus arm, which included one subject that reported 6 episodes of severe hypoglycemia. The time to first event of severe hypoglycemia analysis did reveal a difference between treatment groups, with the MYL IG group having a much shorter mean time (64.4 days) to first occurrence of hypoglycemia compared to the Lantus group (183.6 days). The small number of subjects included in this analysis (Lantus n=9, MYL IG n=7) limits further analysis. The clinical relevance of this finding is unknown. For study 3002, there was only 1 subject in the Lantus group and no subjects in the MYL IG group who reported an event of severe hypoglycemia. The Applicant performed additional analyses of hypoglycemia rate (episodes/30 days), nocturnal hypoglycemia, nocturnal incidence, and other categorical events (documented symptomatic, asymptomatic, probable symptomatic, and relative). These analyses were reviewed but were not included in my review as they were not considered to be useful or as clinically meaningful as severe hypoglycemia. See Sections 12.6.2.4 (3001 study), and Section 12.6.3.5 (3002 study) in the Applicant's Clinical Study Reports for these analyses.

Table 12: Hypoglycemia Events (Trial 3001)

Hypoglycemia Adverse Events	**Lantus (n=278)**		**Mylan IG (n=280)**	
Subjects with Hypoglycemia Events	269	96.8%	273	97.5%
Documented Symptomatic	249	89.6%	249	88.9%
-Severe	13	4.7%	11	3.9%
Episodes of Severe Hypoglycemia Subjects by number of episodes	20	-	14	-
-1 episode	10	-	9	-
-2 episodes	2	-	1	-
-3 episodes	0	-	1	-
-4-6 episodes	1	-	0	-
Time to first event of Severe Hypoglycemia (Days)				
Mean	183.6		64.4	
Median	166.0		72.0	
Min	6.0		3.0	
Max	360.0		166.0	

Source: created using JReview and ADSL.XPT and Hypoglycemia Episodes Analysis datasets for trial 3001.

Table 13: Hypoglycemia Events (Trial 3002)

Hypoglycemia Adverse Events	Lantus (n=282)		Mylan IG (n=276)	
Subjects with Hypoglycemia Events	136	48.2%	130	47.1%
Documented Symptomatic	76	27.0%	75	27 2%
-Severe	1	0.4%	0	0.0%

Source: created using JReview and ADSL.XPT and Hypoglycemia Episodes Analysis datasets for trial 3002.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

There were a total of 464 subjects (83.2%) who experienced at least one TEAE during trial 3001, with 225 subjects (80.4%) in the treatment arm, and 239 subjects (86.0%) in the Lantus arm. Not surprisingly, the most common TEAE was hypoglycemia, occurring in 154 subjects (55.0%) in the treatment arm, and 170 subjects (61.2%) in the Lantus arm, from the "Metabolism and Nutrition disorders" system organ class. The next most common TEAEs were from the SOC "Infections and infestations", occurring in a total of 109 subjects (38.9%) in the treatment arm and 120 subjects (43.2%) in the Lantus arm, which the most common PTs within this SOC being nasopharyngitis, upper respiratory tract infection, and influenza. Imbalances in events not favoring the treatment group occurred in the "Musculoskeletal and connective tissue disorders" SOC, with the most common PT within this SOC being arthralgia, which occurred in 9 subjects (3.2%) in the MYL IG arm, and 2 subjects in the Lantus arm (0.7%). While it is possible the imbalance in events in the "musculoskeletal and connective tissue" SOC is related to an increase in immunogenicity, thereby causing an inflammatory response, this is unlikely, and the overall number of events was too small to represent a clinically important difference.

Table 14: Incidence of Treatment-Emergent Adverse Events Occurring in ≥ 1% of Subjects in Trial 3001 (Safety Population)

System Organ Class Dictionary Derived Term	Lantus n=278		Mylan IG n=280		Total n=558	
METABOLISM AND NUTRITION DISORDERS	**173**	**62.2%**	**157**	**56.1%**	**330**	**39.6%**
HYPOGLYCAEMIA	170	61.2%	154	55.0%	324	38.9%
HYPERGLYCAEMIA	5	1.8%	3	1.1%	8	1.0%
HYPERLIPIDAEMIA	3	1.1%	2	0.7%	5	0.6%
HYPERKALAEMIA	0	0.0%	3	1.1%	3	0.4%

INFECTIONS AND INFESTATIONS	**120**	**43.2%**	**109**	**38.9%**	**229**	**27.5%**
NASOPHARYNGITIS	39	14.0%	25	8.9%	64	7.7%
UPPER RESPIRATORY TRACT INFECTION	33	11.9%	27	9.6%	60	7.2%
INFLUENZA	12	4.3%	12	4.3%	24	2.9%
URINARY TRACT INFECTION	10	3.6%	9	3.2%	19	2.3%
BRONCHITIS	8	2.9%	9	3.2%	17	2.0%
SINUSITIS	8	2.9%	8	2.9%	16	1.9%
GASTROENTERITIS VIRAL	7	2.5%	6	2.1%	13	1.6%
GASTROENTERITIS	6	2.2%	10	3.6%	16	1.9%
VIRAL INFECTION	6	2.2%	5	1.8%	11	1.3%
RHINITIS	5	1.8%	1	0.4%	6	0.7%
RESPIRATORY TRACT INFECTION	3	1.1%	2	0.7%	5	0.6%
RESPIRATORY TRACT INFECTION VIRAL	3	1.1%	1	0.4%	4	0.5%
FUNGAL INFECTION	3	1.1%	3	1.1%	6	0.7%
VULVOVAGINAL MYCOTIC INFECTION	3	1.1%	1	0.4%	4	0.5%
ONYCHOMYCOSIS	3	1.1%	1	0.4%	4	0.5%
PHARYNGITIS	2	0.7%	6	2.1%	8	1.0%
PHARYNGITIS STREPTOCOCCAL	2	0.7%	4	1.4%	6	0.7%
TONSILLITIS	1	0.4%	3	1.1%	4	0.5%
VIRAL UPPER RESPIRATORY TRACT INFECTION	0	0.0%	3	1.1%	3	0.4%
NERVOUS SYSTEM DISORDERS	**28**	**10.1%**	**24**	**8.6%**	**52**	**6.2%**
HEADACHE	14	5.0%	5	1.8%	19	2.3%
DIABETIC NEUROPATHY	3	1.1%	1	0.4%	4	0.5%
CARPAL TUNNEL SYNDROME	0	0.0%	4	1.4%	4	0.5%
NEUROPATHY PERIPHERAL	0	0.0%	3	1.1%	3	0.4%
GASTROINTESTINAL DISORDERS	**26**	**9.4%**	**35**	**12.5%**	**61**	**7.3%**
NAUSEA	6	2.2%	10	3.6%	16	1.9%
TOOTHACHE	5	1.8%	4	1.4%	9	1.1%
DIARRHOEA	4	1.4%	11	3.9%	15	1.8%
VOMITING	2	0.7%	6	2.1%	8	1.0%
INVESTIGATIONS	**22**	**7.9%**	**9**	**3.2%**	**31**	**3.7%**
BLOOD CREATINE PHOSPHOKINASE INCREASED	4	1.4%	1	0.4%	5	0.6%
BLOOD PRESSURE INCREASED	3	1.1%	0	0.0%	3	0.4%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**21**	**7.6%**	**41**	**14.6%**	**62**	**7.4%**
BACK PAIN	6	2.2%	5	1.8%	11	1.3%
ARTHRALGIA	2	0.7%	9	3.2%	11	1.3%
MUSCULOSKELETAL PAIN	3	1.1%	5	1.8%	8	1.0%
TRIGGER FINGER	3	1.1%	0	0.0%	3	0.4%
MUSCLE SPASMS	0	0.0%	4	1.4%	4	0.5%
OSTEOARTHRITIS	0	0.0%	3	1.1%	3	0.4%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**18**	**6.5%**	**23**	**8.2%**	**41**	**4.9%**
LIGAMENT SPRAIN	2	0.7%	3	1.1%	5	0.6%

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**14**	**5.0%**	**23**	**8.2%**	**37**	**4.4%**
COUGH	5	1.8%	6	2.1%	11	1.3%
SINUS CONGESTION	4	1.4%	4	1.4%	8	1.0%
OROPHARYNGEAL PAIN	3	1.1%	6	2.1%	9	1.1%
ASTHMA	0	0.0%	5	1.8%	5	0.6%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**13**	**4.7%**	**16**	**5.7%**	**29**	**3.5%**
PYREXIA	4	1.4%	5	1.8%	9	1.1%
OEDEMA PERIPHERAL	3	1.1%	4	1.4%	7	0.8%
FATIGUE	2	0.7%	4	1.4%	6	0.7%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**12**	**4.3%**	**16**	**5.7%**	**28**	**3.4%**
DERMATITIS CONTACT	4	1.4%	0	0.0%	4	0.5%
CARDIAC DISORDERS	**11**	**4.0%**	**5**	**1.8%**	**16**	**1.9%**
TACHYCARDIA	3	1.1%	0	0.0%	3	0.4%
EYE DISORDERS	**11**	**4.0%**	**8**	**2.9%**	**19**	**2.3%**
DIABETIC RETINOPATHY	5	1.8%	2	0.7%	7	0.8%
VASCULAR DISORDERS	**9**	**3.2%**	**11**	**3.9%**	**20**	**2.4%**
HYPERTENSION	7	2.5%	9	3.2%	16	1.9%
RENAL AND URINARY DISORDERS	**7**	**2.5%**	**9**	**3.2%**	**16**	**1.9%**
MICROALBUMINURIA	0	0.0%	3	1.1%	3	0.4%
PSYCHIATRIC DISORDERS	**6**	**2.2%**	**5**	**1.8%**	**11**	**1.3%**
DEPRESSION	3	1.1%	2	0.7%	5	0.6%
ANXIETY	1	0.4%	3	1.1%	4	0.5%
IMMUNE SYSTEM DISORDERS	**6**	**2.2%**	**5**	**1.8%**	**11**	**1.3%**
SEASONAL ALLERGY	3	1.1%	2	0.7%	5	0.6%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**6**	**2.2%**	**0**	**0.0%**	**6**	**0.7%**
SUBJECTS WITH ANY AE	**239**	**86.0%**	**225**	**80.4%**	**464**	**83.2%**

Source: created using JReview and ADSL.XPT and AE.XPT datasets for trial 3001.

There were a total of 341 subjects (61.1%) who experienced a TEAE, occurring in 177 subjects (64.1%) in the treatment arm, and 164 subjects (58.2%) in the Lantus arm during trial 3002. As in trial 3001, the most common TEAE was hypoglycemia, occurring in 77 subjects (27.9%) in the treatment arm, and 68 subjects (24.1%) in the Lantus arm, from the "Metabolism and Nutrition disorders" system organ class. The next most common TEAEs were from the SOC "Infections and infestations", occurring in a total of 82 subjects (29.7%) in the treatment arm and 66 subjects (23.4%) in the Lantus arm, which the most common PTs within this SOC being upper respiratory tract infection, nasopharyngitis, and urinary tract infection. Hypoglycemia was previously discussed in Section 8.4.4. Apart from hypoglycemia, the largest imbalances in events not favoring the treatment group occurred in the "Infections and Infestations" SOC, Overall, while there were a greater number of TEAEs in the treatment group, with a total of 177

subjects in the treatment group and 164 subjects in the Lantus group, there were no clear patterns in the types of AEs that occurred that would suggest a clinically relevant difference between groups.

Table 15: Incidence of Treatment-Emergent Adverse Events Occurring in ≥ 1% of Subjects in Trial 3002 (Safety Population)

System Organ Class Dictionary Derived Term	Lantus n=282		Mylan IG n=276		Total n=558	
METABOLISM AND NUTRITION DISORDERS	**73**	**25.9%**	**84**	**30.4%**	**157**	**16.5%**
HYPOGLYCAEMIA	68	24.1%	77	27.9%	145	15.2%
INFECTIONS AND INFESTATIONS	**66**	**23.4%**	**82**	**29.7%**	**148**	**15.5%**
UPPER RESPIRATORY TRACT INFECTION	16	5.7%	17	6.2%	33	3.5%
NASOPHARYNGITIS	13	4.6%	11	4.0%	24	2.5%
URINARY TRACT INFECTION	9	3.2%	12	4.4%	21	2.2%
BRONCHITIS	7	2.5%	5	1.8%	12	1.3%
SINUSITIS	5	1.8%	8	2.9%	13	1.4%
INFLUENZA	3	1.1%	7	2.5%	10	1.1%
GASTROENTERITIS VIRAL	3	1.1%	3	1.1%	6	0.6%
GASTROENTERITIS	1	0.4%	5	1.8%	6	0.6%
PHARYNGITIS	1	0.4%	3	1.1%	4	0.4%
PNEUMONIA	0	0.0%	3	1.1%	3	0.3%
VULVOVAGINAL MYCOTIC INFECTION	0	0.0%	3	1.1%	3	0.3%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**30**	**10.6%**	**33**	**12.0%**	**63**	**6.6%**
BACK PAIN	7	2.5%	8	2.9%	15	1.6%
ARTHRALGIA	6	2.1%	4	1.5%	10	1.1%
MUSCULOSKELETAL PAIN	5	1.8%	2	0.7%	7	0.7%
PAIN IN EXTREMITY	4	1.4%	5	1.8%	9	1.0%
GASTROINTESTINAL DISORDERS	**20**	**7.1%**	**28**	**10.1%**	**48**	**5.0%**
DIARRHOEA	6	2.1%	5	1.8%	11	1.2%
VOMITING	5	1.8%	5	1.8%	10	1.1%
NAUSEA	4	1.4%	6	2.2%	10	1.1%
GASTROOESOPHAGEAL REFLUX DISEASE	3	1.1%	1	0.4%	4	0.4%
ABDOMINAL PAIN	1	0.4%	4	1.5%	5	0.5%
DYSPEPSIA	0	0.0%	4	1.5%	4	0.4%
CONSTIPATION	0	0.0%	3	1.1%	3	0.3%
NERVOUS SYSTEM DISORDERS	**23**	**8.2%**	**24**	**8.7%**	**47**	**4.9%**
HEADACHE	10	3.6%	8	2.9%	18	1.9%
DIZZINESS	7	2.5%	4	1.5%	11	1.2%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**16**	**5.7%**	**19**	**6.9%**	**35**	**3.7%**
OEDEMA PERIPHERAL	6	2.1%	2	0.7%	8	0.8%

FATIGUE	3	1.1%	4	1.5%	7	0.7%
INJECTION SITE PAIN	2	0.7%	3	1.1%	5	0.5%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**22**	**7.8%**	**17**	**6.2%**	**39**	**4.1%**
COUGH	10	3.6%	4	1.5%	14	1.5%
OROPHARYNGEAL PAIN	5	1.8%	5	1.8%	10	1.1%
RESPIRATORY TRACT CONGESTION	0	0.0%	3	1.1%	3	0.3%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**17**	**6.0%**	**13**	**4.7%**	**30**	**3.2%**
CONTUSION	4	1.4%	1	0.4%	5	0.5%
LACERATION	4	1.4%	0	0.0%	4	0.4%
VASCULAR DISORDERS	**3**	**1.1%**	**10**	**3.6%**	**13**	**1.4%**
HYPERTENSION	3	1.1%	6	2.2%	9	1.0%
INVESTIGATIONS	**10**	**3.5%**	**10**	**3.6%**	**20**	**2.1%**
LIPASE INCREASED	1	0.4%	4	1.5%	5	0.5%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**10**	**3.5%**	**7**	**2.5%**	**17**	**1.8%**
PRURITUS	3	1.1%	1	0.4%	4	0.4%
RASH	3	1.1%	3	1.1%	6	0.6%
PSYCHIATRIC DISORDERS	**6**	**2.1%**	**5**	**1.8%**	**11**	**1.2%**
RENAL AND URINARY DISORDERS	**8**	**2.8%**	**5**	**1.8%**	**13**	**1.4%**
DYSURIA	3	1.1%	0	0.0%	3	0.3%
NEPHROLITHIASIS	0	0.0%	3	1.1%	3	0.3%
EYE DISORDERS	**4**	**1.4%**	**4**	**1.4%**	**8**	**0.8%**
CARDIAC DISORDERS	**4**	**1.4%**	**3**	**1.1%**	**7**	**0.7%**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**3**	**1.1%**	**2**	**0.7%**	**5**	**0.5%**
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**3**	**1.1%**	**2**	**0.7%**	**5**	**0.5%**
IMMUNE SYSTEM DISORDERS	**7**	**2.5%**	**2**	**0.7%**	**9**	**0.9%**
SEASONAL ALLERGY	5	1.8%	1	0.4%	6	0.6%
SUBJECTS WITH ANY AE	**164**	**58.2%**	**177**	**64.1%**	**341**	**61.1%**

Source: created using JReview and ADSL.XPT and AE.XPT datasets for trial 3002.

8.4.6. Laboratory Findings

There were no clinically important differences in laboratory data between treatment groups

8.4.7. Vital Signs

There were no clinically significant changes in mean values from baseline for either treatment group for vital signs at any times points during either trial.

8.4.8. Electrocardiograms (ECGs)

ECGs were assessed at baseline, as well as at Week 24, and in Trial 3001, at Week 52. In Trial 3001, there was 1 subject in the MYL IG group that had a normal ECG at baseline, who subsequently had an abnormal ECG at Week 24. There were no abnormal ECGs at Week 52. There were no subjects in the Lantus group with clinically significant abnormal ECGs during the 3001 trial. Additional information on the ECG abnormalities was not provided. In Trial 3002, there were 2 subjects in the MYL IG group that had normal ECGs at baseline, subsequently developed abnormal ECGs at Week 24. One subject was reported to have a "cardiac arrhythmia", and the second subject was reported to have a "nodal rhythm". Both events were reported as AEs, and both events resolved without treatment. Although there was a small imbalance in ECG abnormalities in the MYL IG group, with 1 subject in the 3001 trial and 2 subjects in the 3002 trial, ECG-related safety signals would not be expected with insulin glargine, as the listed drug is not known to have ECG-related safety signals, and in the opinion of this reviewer, it is likely the imbalances in ECG findings in the MYL IG group were due to chance.

8.4.9. QT

There were no patients reported with any clinically significant QT abnormalities.

8.4.10. Immunogenicity

The Applicant analyzed anti-drug antibodies (ADA) using a multi-tiered process, with a screening tier, confirmatory tier, and characterization tier. Due to the potential structural differences between MYL IG and Lantus, resulting from different host cells used for production, a two assay approach was utilized. The assays were identical with the exception of a unique radiolabeled tracer for both Lantus and MYL IG. The total anti-drug antibody and insulin cross reactivity results were reported in terms of their presence (positive or negative), along with the percent specific binding (%SB), which is the relative amount of antibody present in the samples. Drug-specific ADA were determined by gamma counting of ADA complex formation, and is expressed as a percentage of bound to total radioactivity (%B/T).

For trial 3001, the majority of patients (73.2% and 73.7% for the MYL IG and Lantus groups, respectively) were positive for antibodies at baseline, while in the 3002 trial, only a minority of patients (19.2% and 21.3% for the MYL IG and Lantus groups, respectively) were positive at baseline. Antibody positivity is summarized in Table 16 and Table 17. Overall, for both trials 3001 and 3002, the incidence of positive responses for both total ADA and insulin cross-reactive antibodies were similar between treatment groups at all scheduled visits for both assays.

The changes in drug-specific ADA %B/T, as well as total anti-drug and insulin cross-reactive

antibody %SB were reviewed. The drug-specific ADA %B/T was near zero for both MYL IG and Lantus assays, at all scheduled visits, which demonstrates the ADA was cross reactive with both MYL IG and Lantus, for both trials 3001 and 3002.

There was no difference between treatment groups for change from baseline in mean total insulin antibody %SB at any scheduled visit for the 3001 trial. For the 3002 trial, there was a small but statistically significant increase from baseline in the mean (±SD) total anti-drug antibody in the MYL IG treatment group at Week 12 (1.92 ± 12.54; p = 0.015) and Week 24 (1.78 ± 9.65; p = 0.004) using the MYL IG assay. When compared to the Lantus group, the difference was also statistically significant at Week 12 (p=0.049), although not at Week 24 (p=0.171). There was a similar trend using the Lantus assay, although the differences between groups were not significant.

The insulin cross-reactive antibody %SB did not demonstrate a statistically different change from baseline between the two treatment groups at any scheduled visits for the 3001 trial. However, in the 3002 trial, there was a statistically significant increase from baseline in the mean (±SD) insulin cross-reactive antibodies in the MYL IG treatment group at Week 12 (1.75 ± 11.68; p = 0.017) and Week 24 (1.63 ± 9.11; p = 0.006) using the MYL IG assay. When compared to the Lantus group, the difference was also statistically significant at Week 12 (p=0.044), although not at Week 24. There was a similar trend using the Lantus assay, although the differences between groups were not significant. It is important to note, however, that the Lantus group had a higher mean baseline value, and it may be that the increase from baseline for the MYL IG group was related to the difference in baseline values. In addition, while the mean changes from baseline for the MYL IG group were significant, the median changes were not, and suggest the changes in mean values were due to a small number of outliers. Overall, the data do not suggest a clinically important increase in antibody titers.

Table 16: Proportions of Subjects with Positive Total Anti-Drug and Insulin Cross-Reactive Antibodies in the 3001 Trial

	MYL IG Assay			Lantus Assay		
	MYL IG N=280	**Lantus N=278**	**p-value**	**MYL IG N=280**	**Lantus N=278**	**p-value**
Total Anti-Drug antibodies						
Baseline Positive	205 (73.2)	205 (73.7)	0.923	209 (74.6)	221 (79.5)	0.355
Week 12 Positive	204 (72.9)	200 (71.9)	>0.999	203 (72.5)	208 (74.8)	0.226
Week 24 Positive	194 (69.3)	197 (70.9)	0.765	209 (74.6)	206 (74.1)	0.834
Week 36 Positive	184 (65.7)	179 (64.4)	0.918	191 (68.2)	183 (65.8)	0.830
Week 52 Positive	190 (67.9)	185 (66.5)	0.833	196 (70.0)	190 (68.3)	>0.999
Insulin cross-reactive antibodies						
Baseline Positive	204 (72.9)	211 (75.9)	0.431	201 (71.8)	217 (78.1)	0.196
Week 12 Positive	205 (73.2)	200 (71.9)	>0.999	198 (70.7)	203 (73.0)	0.238
Week 24 Positive	194 (69.3)	200 (71.9)	0.548	200 (71.4)	198 (71.2)	0.920

Week 36 Positive	188 (67.1)	178 (64.0)	0.755	186 (66.4)	175 (62.9)	0.605
Week 52 Positive	189 (67.5)	186 (66.9)	>0.999	188 (67.1)	181 (65.1)	0.918

Table 17: Proportions of Subjects with Positive Total Anti-Drug and Insulin Cross-Reactive Antibodies in the 3002 Trial

	MYL IG Assay			Lantus Assay		
	MYL IG N=276	**Lantus N=282**	**p-value**	**MYL IG N=276**	**Lantus N=282**	**p-value**
Total Anti-Drug antibodies						
Baseline Positive	53 (19 2)	60 (21.3)	0.598	61 (22.1)	66 (23.4)	0.687
Week 12 Positive	61 (22.1)	64 (22.7)	0.918	69 (25.0)	71 (25.2)	>0.999
Week 24 Positive	70 (25.4)	76 (27.0)	0.693	75 (27 2)	77 (27.3)	0.922
Insulin cross-reactive antibodies						
Baseline Positive	57 (20.7)	59 (20.9)	>0.999	63 (22.8)	65 (23.0)	0.920
Week 12 Positive	60 (21.7)	62 (22.0)	>0.999	61 (22.1)	65 (23.0)	0.760
Week 24 Positive	72 (26.1)	72 (25.5)	0.921	70 (25.4)	70 (24.8)	>0.999

Source: Adapted from the Applicant's Clinical Study Report for the 3001 trial, Tables 12-13, 14.4.1, 14.4.2, and from the 3002 trial, Tables 12-8, 14.4.1, and 14.4.2

In order to evaluate for the possibility of antibody neutralization, the Applicant reviewed subjects that met the criteria for an increase over 10% in insulin cross-reactive ADA, an increase in HbA1c over 0.2%, and an increase in insulin dose. For both trials, there was a small percentage of subjects who met these criteria in both treatment groups, and the number of subjects increased throughout the trial duration. However, there was no major difference in the number of subjects who met the criteria between treatment groups.

Based on the review of the immunogenicity data, the data overall does not demonstrate a clinically important difference in efficacy or safety, in the opinion of this reviewer.

Table 18: Incidence of Patients Meeting the Criteria for Insulin Cross-Reactive Antibody, HbA1c and Dose Increase by Visit (3001 Trial)

Visit	Characteristics	MYL IG (N = 280) n (%)	Lantus (N = 278) n (%)	p-value
Week 12	Yes	12 (4.3)	12 (4.3)	>0.999
	No	265 (94.6)	259 (93.2)	
	Missing	3	7	
Week 24	Yes	15 (5.4)	17 (6.1)	0.718
	No	254 (90.7)	248 (89.2)	
	Missing	11	13	
Week 36	Yes	25 (8.9)	18 (6.5)	0.341
	No	241 (86.1)	242 (87.1)	
	Missing	14	18	
Week 52	Yes	28 (10.0)	22 (7.9)	0.460
	No	235 (83.9)	233 (83.8)	
	Missing	17	23	

Source: Table 12-15 from Applicant's Clinical Study Report, 3001 trial

Table 19: Incidence of Patients Meeting the Criteria for Insulin Cross-Reactive Antibody, HbA1c and Dose Increase by Visit (3002 Trial)

Visit	Characteristics	MYL IG (N=276) n(%)	Lantus (N=282) n(%)	P-Value
Week 12	Yes	6 (2.2)	6 (2.1)	>.999
	No	254 (92.0)	259 (91.8)	
	Missing	16	17	
Week 24	Yes	18 (6.5)	15 (5.3)	.592
	No	227 (82.2)	235 (83.3)	
	Missing	31	32	

Source: Table 12-9 from Applicant's Clinical Study Report, 3002 trial

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hypersensitivity Reactions

In order to evaluate hypersensitivity reactions during the 3001 and 3002 trials, standardized MedDRA queries (SMQs) were performed using the following terms: "hypersensitivity reactions" (broad and narrow), "angioedema" (narrow), "severe cutaneous adverse reaction" (broad), and "anaphylactic reaction" (broad and narrow).

For the 3001 trial, there were a greater number of hypersensitivity reactions in the MYL IG treatment arm, while in the 3002 trial, there were a greater number of hypersensitivity reactions in the Lantus treatment arm. Overall, I do not think these events represent an increase in hypersensitivity reactions for MYL IG. Many of the events identified by the SMQ do not represent a clinically meaningful severe hypersensitivity event, but rather a more benign event that may not be drug related. For example, the majority of events identified as "hypersensitivity reactions" for MYL IG were seasonal allergy and eczema, while asthma and cough made up the vast majority of "anaphylactic reactions".

Table 20: Standardized MedDRA Queries for Hypersensitivity Reactions (Trial 3002)

	Trial 3001				**Trial 3002**			
Standardized MedDRA query terms	**Lantus n=278**		**Mylan IG n=280**		**Lantus n=282**		**Mylan IG n=276**	
	Events	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**
HYPERSENSITIVITY REACTIONS								
BROAD	**16**	**15**	**29**	**22**	**20**	**18**	**9**	**7**
NARROW	**9**	**8**	**13**	**10**	**11**	**10**	**6**	**5**
ANGIOEDEMA								
NARROW	**3**	**2**	**1**	**1**	**3**	**3**	**1**	**1**
SEVERE CUTANEOUS ADVERSE REACTION								
BROAD	**0**	**0**	**3**	**3**	**0**	**0**	**1**	**1**
NARROW	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
ANAPHYLACTIC REACTION								
BROAD	**15**	**13**	**17**	**14**	**20**	**17**	**13**	**10**
NARROW	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Source: created using MAED and standardized MedDRA queries

Injection site reactions are also a known safety concern associated with the use of insulin

products. There was only 1 subject with the reported event of “injection site pain” in the MYL IG group in the 3001 trial. There were 3 subjects in the MYL IG group and 2 subjects in the Lantus group with the reported event of “injection site pain”, and 1 subject in each treatment group with the reported event of “injection site reaction” in the 3002 trial. Overall, the number of subjects is very small, and the data does not suggest a safety concern.

8.6. Safety Analyses by Demographic Subgroups

The Applicant did not perform any specific safety analyses by demographic subgroup and the trials were not powered to reach conclusions on safety with respect to demographic subgroups. Due to the limitations of the demographic groups included in the study, specifically age and racial and ethnic subgroups, the subgroup analysis was limited to gender. As the most common safety concern for the trials was hypoglycemia, these events were re-reviewed in the context of gender, however the data did not show any differences in outcomes with respect to gender.

8.7. Specific Safety Studies/Clinical Trials

None.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There were no new evaluations of human carcinogenicity performed as part of this submission.

8.8.2. Human Reproduction and Pregnancy

Only females of childbearing potential who were willing to use either oral contraceptives or two acceptable forms of contraception were included in the trials, limiting the potential for pregnancies during this trial. In the 3001 trial, there were 5 pregnancies reported during the study that led to the premature discontinuation of the subjects. Of the 5 pregnancies, 3 had normal healthy newborns, while 1 pregnancy (MYL IG treatment group) was electively terminated due to the finding of spina bifida, and 1 pregnancy (Lantus treatment group) resulted in a newborn with septal hypertrophic cardiomyopathy, mitral insufficiency, tricuspid insufficiency, and a permeable foramen ovale. There were no pregnancies reported in the 3002 trial.

8.8.3. Pediatrics and Assessment of Effects on Growth

As the application does not contain any elements that would trigger the Pediatric Research Equity Act (PREA), it was determined by the FDA that pediatric studies are not required.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant did not report any events of study medication overdose, however potential accidental drug overdose events would likely result in hypoglycemia, and these events are further discussed in 8.4.4. Drug abuse potential for MYL IG was not assessed, and there is no evidence to suggest the potential for abuse, dependency, withdrawal, or rebound with insulin glargine products, including MYL IG.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The risks associated with use of MYL IG, and insulin products in general, include hypoglycemia, hypersensitivity reactions, and injection site reactions. These risks are further discussed in 8.4.4 and 8.5.1, respectively.

8.9.2. Expectations on Safety in the Postmarket Setting

No new safety signals were identified in the last DSUR.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.10. Integrated Assessment of Safety

The safety findings for the two trials were generally consistent with the safety findings of the listed drug, Lantus. The known risks associated with use of insulin products include hypoglycemia, hypersensitivity, and injection site reactions. Safety findings observed in the two trials include hypoglycemia, which was the most common TEAE in both trials, and was also the most common SAE in the 3001 trial, as well as gastrointestinal disorders (pancreatitis and gastric ulcer), which were the most common SAE observed in the 3002 trial. There were a total of three deaths during the trials (two in the MYL IG group and 1 in the Lantus group), at least one of which was the result of hypoglycemia. The overall incidence of adverse events was similar between treatment groups in both trials, and there were no new safety concerns identified.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Not applicable as I am recommending a Complete Response.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategy is recommended for this NDA.

12. Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments recommended for this NDA.

13. Appendices

13.1. References

1. Lantus [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; July 17, 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021081s063lbl.pdf
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7. American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment. Sec. 8. In Standards of Medical Care in Diabetes-2017. Diabetes Care 2017;40:S64-S74.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1,175		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0		

Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from 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) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

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04/30/2018

PATRICK ARCHDEACON
04/30/2018