

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210605Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA	210605 / 0045
Submission Dates	02/28/2019 (Class 2 resubmission after complete response dated 05/17/2018)
Brand Name	Semglee
Generic Name	Insulin glargine (MYL-1501D)
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Mylan GmbH
Formulation; Strength; Presentation	Solution for subcutaneous injection; 100 units/mL; 10 mL vial and 3mL cartridge
Relevant IND	105279
Indication	Long-acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus
OCP Review Team	Jing Niu, M.D., Manoj Khurana, Ph.D., Suryanarayana Sista, Ph.D.

This addendum provides clinical pharmacology clarification to questions raised by the CDTL regarding Study MYL-1501D-1001, MYL-1501D-1003, and MYL-1501D-1004.

The clinical pharmacology review for the resubmission of NDA 210605 was posted to DARRTS on July 25, 2019 by Dr. Jing Niu (*DARRTS, Reference ID: 4468057*). In this review OCP concluded that the clinical pharmacology data findings from Studies MYL-1501D-1004 and MYL-1501D-1003 were acceptable.

Below are the responses to CDTL's questions from OCP:

- 1) Did MYL-1501D-1001 (the study OCP reviewed in the original submission) have similar issues as GLARGCT1001111 and MYL-1501D-1004 with regard to unusable data? Was the more sensitive assay used in MYL-1501D-1003 or the less sensitive assay used in MYL-1501D-1004?**

OCP response: Study MYL-1501D-1001 had less than 10% unusable data for PK and PD, thus we accepted the results of the study. Study GLARGCT1001111 had a high proportion of unusable data (more than 30%), however, since this study did not use the to-be-marketed formulation, we considered it as only supportive study.



Study MYL-1501D-1003 used a more sensitive assay (lower LOQ) and is reflected in more usable PK data in the study. Please refer to Table 11 in the Clinical Pharmacology review posted in DARRTS on July 25, 2019 (*Reference ID: 4468057*) for more details regarding the bioanalytical assays used for studies MYL-1501D-1001, MYL-1501D-1003, and MYL-1501D-1004.

2) Study MYL-1501D-1003 did not address any deficiencies in the complete response letter for the original submission. Why do OCP see MYL-1501D-1003 as pivotal?

OCP response: Study MYL-1501D-1003 was deemed as pivotal since the to-be-marketed product (process VI) was used. This study confirmed the findings of Study MYL-1501D-1001 in the original submission and was viewed in the framework of the totality of evidence from a Clinical Pharmacology perspective.

We agree that Study MYL-1501D-1003 did not address any deficiencies in the complete response letter for the original submission, and we also had not requested this study. One possible reason for the Sponsor to conduct Study MYL-1501D-1003 is that in the review cycle of the original submission, the review team noted that some secondary PD endpoints in study MYL-1501D-1001 did not meet the bioequivalence (BE) criteria. In a face to face meeting, the review team conveyed to the Sponsor (*meeting minutes in DARRTS dated Sep 6, 2017, Reference ID: 4149214*) that failure of PD endpoints meeting the BE criterion was a review issue which may reflect in asking for additional Phase 3 clinical trial. The Sponsor volunteered to conduct a new study (MYL-1501D-1003) to replicate Study MYL-1501D-1001. Note that failure of secondary PD endpoints to meet BE criteria is not critical to the acceptability of overall BE findings from a clinical pharmacology perspective.

3) Did MYL-1501D-1004 definitively have enough power to support conclusions despite the high number of unusable PK profiles? What is your rationale for concluding this?

OCP response: Based on the following, we believe this study had enough power to support the conclusion.

- After exclusion of unusable PK profiles, study MYL-1501D-1004 still met the BE criteria, indicating that the study was over powered.
- Overpowering is not unusual for PK/PD Clamp studies as Applicants usually calculate the sample size based on the worst-case scenario (generally using the highest observed variability in PK and PD and accounting for maximum dropout rate and exclusion rate) to ensure the study could be used for BE assessment. The sample size in Study MYL-1501D-1004, was calculated assuming a CV% of 66% based on historical data, while the actual CV% was less than 50% in the study. The sponsor also added 6 additional subjects to account for dropout and data exclusion (as specified in the protocol).



- An additional rationale is based on our experience with PK/PD clamp studies for insulin. Historically, the sample size that have been used for replicate crossover PK/PD clamp studies for insulin is n=24. In the current NDA, even after exclusion of unusable PK data, evaluable PK data from 40 subjects were available for the BE analysis.

4) How can we be sure that the high unusable PK data in MYL-1501D-1004 is related to sensitivity of the assay and not that the drug isn't being absorbed?

OCP response: As shown in the table below, all 90 PD observations from the replicate crossover design from a total of 45 subjects were included in the PD analysis, including from those subjects with unusable PK observations. This could rule out the hypothesis that the drug did not get absorbed.

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: Table 4 in the Clinical Pharmacology review posted in DARRTS on July 25, 2019 (Reference ID: 4468057)

Because of the uniqueness of issues related to unusable data, the available data and recommendations were discussed with the senior leadership in Clinical Pharmacology. There was consensus that scientifically results are acceptable to establish PK/PD comparability between MYL-1501D Process VI formulation in vial (with polysorbate) and MYL-1501D Process VI formulation in cartridges (without polysorbate).

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/

JING NIU
08/22/2019 09:08:13 AM

SURYANARAYANA M SISTA
08/22/2019 09:11:04 AM
Signing on behalf of Manoj Khurana

Clinical Pharmacology Team-Leader Memo

NDA #: 210605
Submission Type: 505(b)(2)
Sponsor: Mylan
Brand name (Drug): SEMGLEE (Insulin Glargine)
Memo Date: 08/16/2019
Reviewer: Manoj Khurana, Ph.D.
Through: Chandrahas Sahajwalla, Ph.D.
OCP Division: DCP-2
Subject: Comparative Immunogenicity of SEMGLEE

Introduction

Exogenous insulin therapy is known to be immunogenic since its inception. Publicly available information on insulins and published literature do not indicate any clinically relevant effects of immunogenicity on efficacy as measured by change in HbA1c. The approved insulin labels do not carry any specific dosing recommendations for altered insulin daily dose requirements based on antibody titers. Although immunogenicity is prevalent across labelled products with a variety of routes of administrations (IV, SC, and Inhaled), the immune response is perhaps most robust with inhaled insulin. Even in the context of inhaled insulin, however, the observed immunogenicity is not associated with any clinical consequence¹.

Given the current state of knowledge on heterogeneity in antibody (hereafter ADA: anti-drug antibody, also referred to as AIA: anti-insulin antibody) type/titer and affinity, and the role of assay type in ADA characterization², the assessment of drug-specific (DS-ADA), cross-reacting (CR-ADA), and total ADA typically applied during drug development is somewhat facile. However, valuable insights can nonetheless be derived from measuring circulating ADAs (DS-ADA, CR-ADAs etc.) and determining whether these ADAs have an impact on clinical pharmacology/clinical measures.

While analytical methods can detect DS-ADA and CR-ADA, it is important to consider that all insulins can generate cross-reacting antibodies to human insulin. Since insulin analogs share majority of the human insulin backbone being > 95% homologous with regular human insulin being 100% homologous, the mutual cross-reactivity of antibodies is inevitable³.

The body weight consideration for insulin dose is well established, typical of any endocrine hormone replacement therapy, knowing the association of hepatic glucose production and glucose utilization with body weight/size. However, measurement of insulin concentrations is not routine in typical Phase 3 trials. Often in absence of concentration data, insulin dose is relied upon to assess the impact of factors/co-factors and specifically in the context of immunogenicity, as an indirect measure of clinically relevant impact on insulin systemic exposure and response, e.g., in

¹Antibody Response to Inhaled Insulin in Patients with Type 1 or Type 2 Diabetes. An Analysis of Initial Phase II and III Inhaled Insulin (Exubera) Trials and a Two-Year Extension Trial. S. Edwin Fineberg et al., *The Journal of Clinical Endocrinology & Metabolism*, Volume 90, Issue 6, 1 June 2005, Pages 3287–3294.

² Immunological Responses to Exogenous Insulin. S. Edwin Fineberg et al. *Endocrine Reviews* 28(6):625–652.

³Satish K. Garg et al. *DIABETES TECHNOLOGY & THERAPEUTICS*, Volume 19, Number 9: 516-526, 2017

situations of neutralizing effect of ADA on systemic insulin concentrations or immunogenic resistance driven increase insulin dose requirement – although both are noted as vanishingly rare for insulins in the published literature².

Further, for exogenous insulin therapy in general, in addition to the body weight effect on individual dose requirements, variety of sources are known to influence inter and intra-individual variability in PK and Glycemic Response. This together with number of other factors contribute to the challenges for optimal insulin use^{4,5}. These unique characteristics are applicable during controlled clinical evaluation setting invariably for test and reference treatments. Therefore, prompting a curiosity whether they could pose a challenge in teasing out any additional/specific factor (e.g. immunogenicity) towards a clinically relevant impact or difference in clinical trials.

Purpose

This memo summarizes additional Clinical Pharmacology assessments conducted during the review on scientific and regulatory aspects of exogenous insulin immunogenicity as reported in the data for SEMGLEE under NDA 210605. The memo serves as addendum to the primary clinical pharmacology review conducted by Dr. Jing Niu for the comparative euglycemic clamp PK/PD studies.

The memo comments on data from Trial 3001 and the data from clinical study submitted in the NDA resubmission (3004) where, intended commercial product (API; Insulin glargine, manufactured using process VI) was compared to Insulin glargine manufactured using process V, to establish the clinical bridge to justify the relevance of data comparing insulin glargine product using Process V to US-Lantus in the comparative clinical studies (3001 and 3002) submitted with the original NDA. The appropriateness of the clinical bridging is deferred to the acceptability of the trials 3001 (Original submission) and 3004 (resubmission) data by Clinical and Statistical review disciplines.

The memo is not intended to debate appropriate strategy to introduce a change in the intended commercial product, the agency's thinking on this matter is already reflected in the final recommendations and requirements communicated to the applicant in the complete response issued for the original NDA submission on 05/27/2018. However, the applicant's choice to pursue the intended commercial formulation from Process VI for obtaining relatively purified (b) (4) form of the API, and subsequently conducting a clinical pharmacology and clinical comparison with Process V formulation (focus of resubmission review), has generated sequential data from two comparative clinical trials that could, in retrospect, speak to the value of the information that these comparisons brought from a scientific perspective for immunogenicity of SEMGLEE.

While the detailed clinical assessments of immunogenicity and specifics of trial elements for SEMGLEE are captured in the Clinical reviews, this memo discusses some translational aspects of the information from the same trials utilizing graphical analysis of two or more factors of interest.

⁴Variability of Insulin Absorption and Insulin Action. Lutz Heinemann. DIABETES TECHNOLOGY & THERAPEUTICS. Volume 4, Number 5: 673-682, 2002.

⁵Variability of glucose-lowering effect as a limiting factor in optimizing basal insulin therapy: a review. J. Vora & T. Heise. Diabetes, Obesity and Metabolism 15: 701-712, 2013.

The information from analysis of select data from the following Clinical Trials are used interchangeably in this memo to highlight the discussion points:

- a. Trial 3001
- b. Trial 3004

1. What are the unique aspects of multi-dose injection (MDI) trial designs in subjects with type 1 diabetes from immunogenicity evaluation perspective?

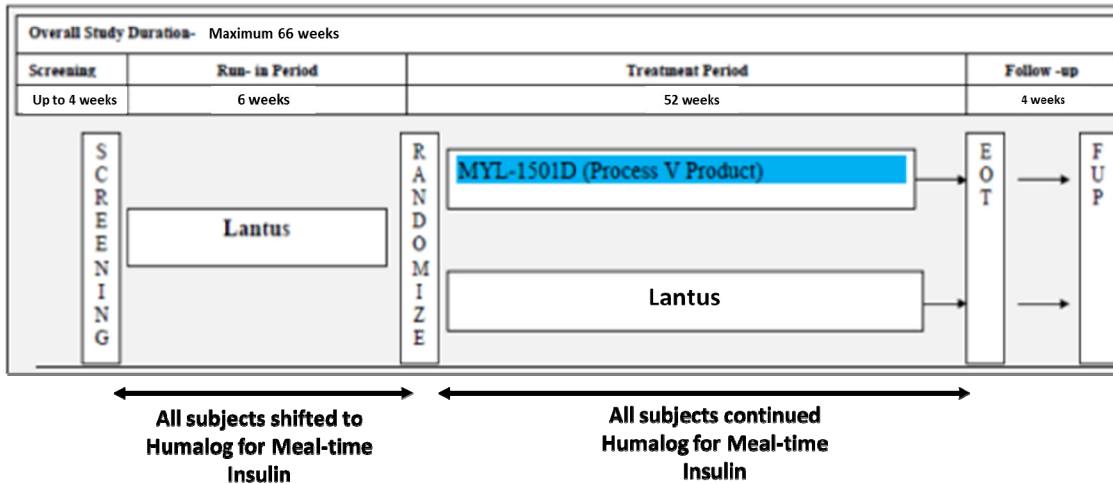
As typical of an insulin MDI trial in T1DM, SEMGLEE clinical trials 3001 and 3004 also incorporated a basal-bolus insulin regimen and tested two structurally different insulin products within a subject. This design is generally followed to optimize the glycemic control and mimic endogenous insulin secretory pattern.

From a comparative immunogenicity assessment and an immune response perspective, this aspect is unique and important consideration for SEMGLEE comparability trials.

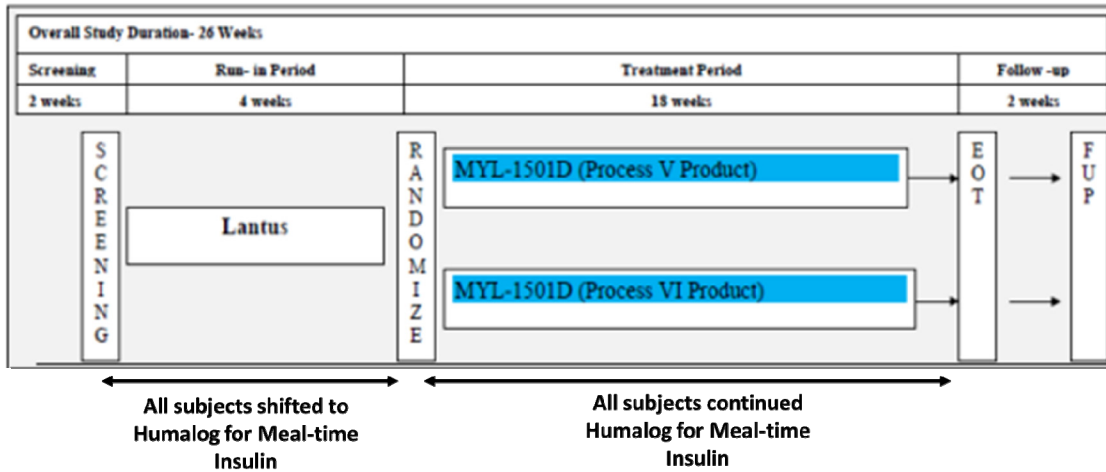
The schematic of trials 3001 and 3004 are shown below.

Figure 1. Schematic of MDI Trial Designs (Adapted from trial schematics from respective CSRs)

Trial 3001 (original NDA):



Trail 3004 (resubmission):



Abbreviations: EOT = End-of-Treatment visit; FUP = Follow-up visit;

As typical of T1DM MDI trials in insulin drug development, SEMGLEE trials recruited subjects who had progressed into the disease beyond 1 year and thus had well established prior insulin use. A good account of prior history of insulin use was documented by the applicant in majority of the trial subjects and a thorough analysis of this data was conducted by this reviewer to assess the heterogeneity in prior insulin combination therapy in the trial population. The figure below shows that trial subjects represented a population with reasonably heterogenous prior insulin use. Since protocol specified minimum 3 month use of Lantus with $\pm 15\%$ dose variation during 3 months prior to screening, almost all subjects, for whom prior insulin use information was available in the applicant's data-sets, had ongoing use of Lantus with different bolus insulins (right panel for Trial 3001 Figure).

Figure 2. Prior Insulin Use in Trial 3001 Population (Ongoing=Yes for Insulin in Use at time of screening)

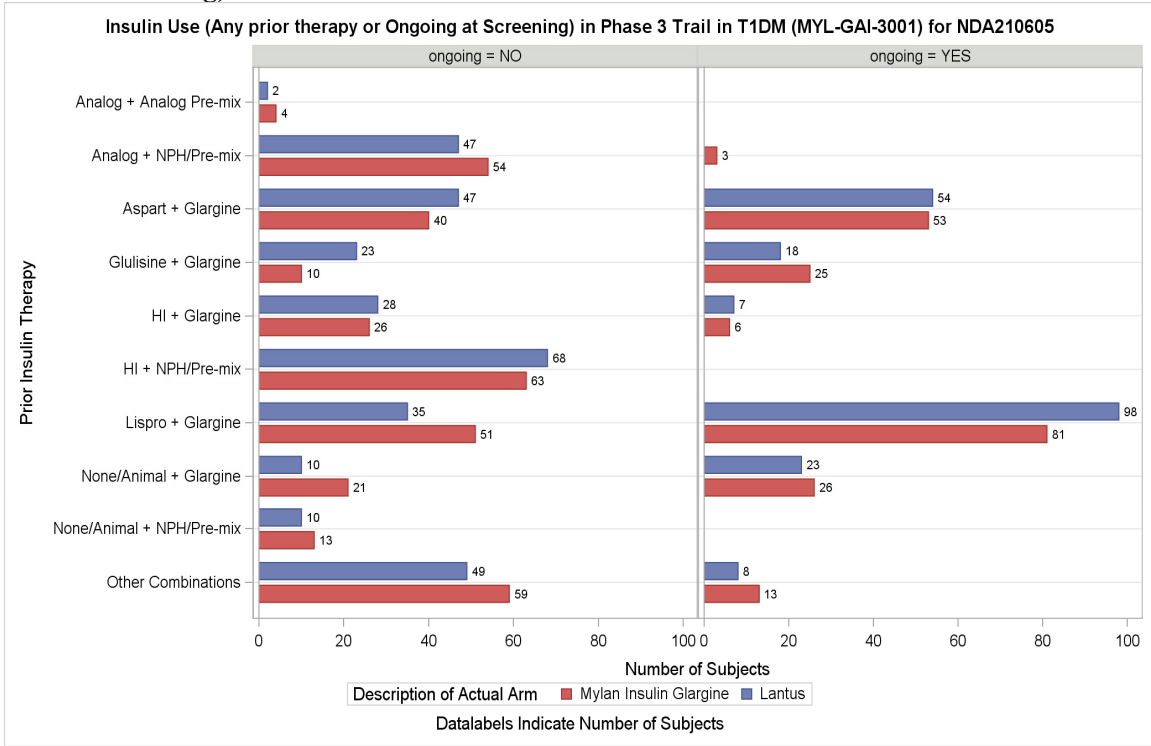
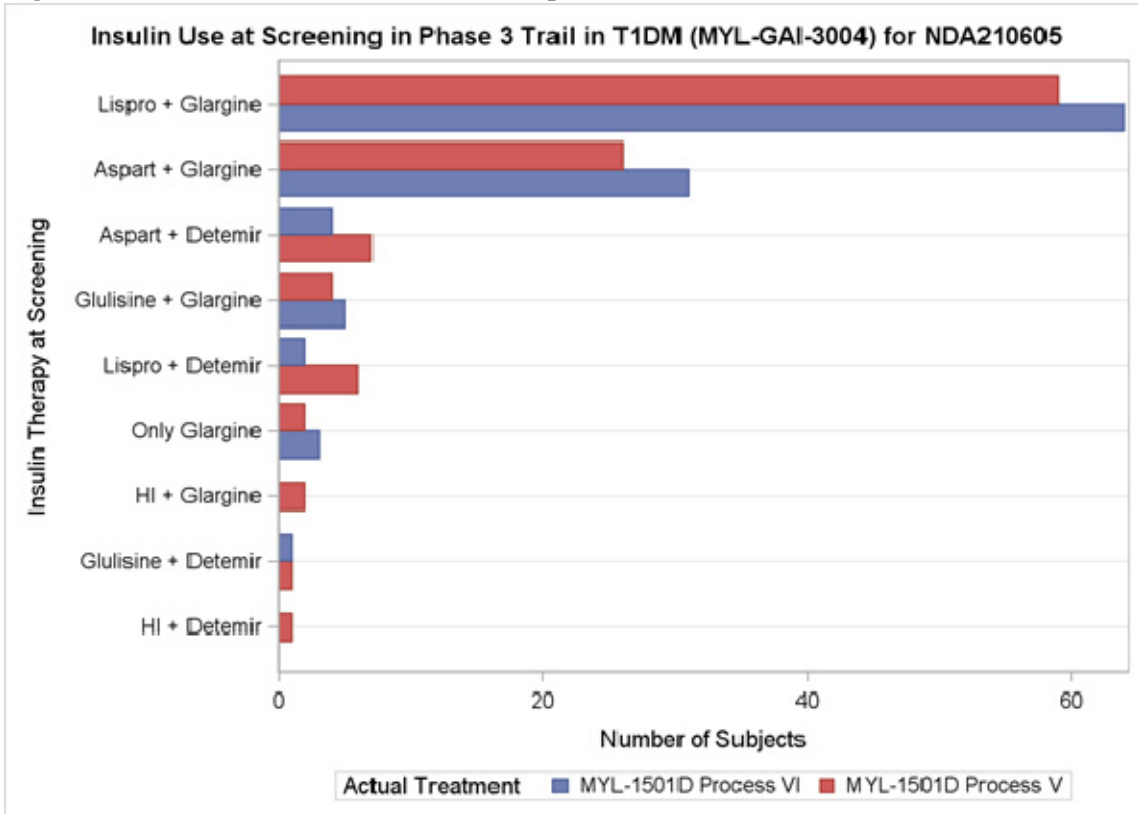


Figure 3. Prior Insulin Use in Trial 3004 Population



Some pros and cons of this design are listed below from a pure translational perspective:

Pros:

- From a robustness perspective, this is reasonably close to mimicking a real-life scenario testing for a newly introduced insulin
- Trial subjects are representative of the intended T1DM population
- The run-in phase when subjects are moved from prior insulin combination to the insulin under evaluation (almost always specified in the protocols as a transition on unit-to-unit dose basis from prior therapy) is perhaps an important time window as well to observe dose and safety related aspects of shifting patients to Insulin Glargine+Humalog
- While the focus is always on the test insulin in such trials, as is here on SEMGLEE, and bolus insulin component is regarded as non-investigational medical product (NIMP) for regulatory purpose, the data on Humalog (prandial insulin) co-use on its contribution to safety/efficacy inevitably exists for scientific purpose. Same would apply for a prandial insulin trial
- For the above last two points, the dose-time information on basal and bolus dose will be very informative towards real-life use of SEMGLEE (and perhaps Humalog as well if one were to fully leverage the trial results from a therapeutic use perspective)

Cons:

- The design poses some challenges in interpreting the immunogenicity data at baseline and change thereafter
- The week 4-6 run-in phase assumes a wash-out of immunogenicity of prior combinations to some altered state of immunogenicity to Humalog/Lantus combination to balance the baseline ADA status – the subsequent immunogenicity data is still captured in the presence of a combination use of Humalog and SEMGLEE or Lantus
- Transition to a new combination from partially identical (e.g. prior Humalog use at screening), identical (e.g., possible single switch to SEMGLEE from Lantus/another insulin glargine as a basal insulin component and Humalog as bolus component at screening) or totally new basal-bolus combination gets evaluated in this trial setting

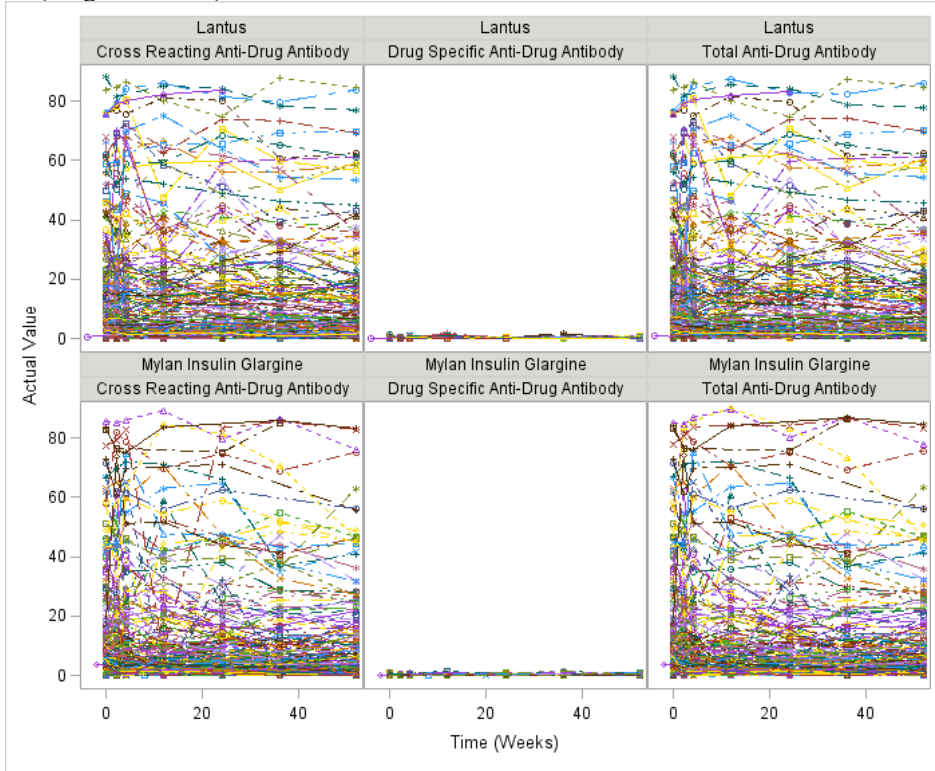
2. What are the unique aspects of exogenous insulin immunogenicity as it applies to SEMGLEE?

For detailed information on the technical and clinical safety aspects of immunogenicity, refer to the OBP and clinical reviews, respectively. The information below summarizes results of the exploratory analysis that was conducted by this reviewer to understand the nature of immune response at individual and population levels comparing SEMGLEE and LANTUS. The immunogenicity data (ADA titers) was graphically analyzed to evaluate the following:

- a. Individual level ADA titers and change from baseline by treatment over trial duration
- b. Change from baseline at end-point by ADA type by treatment
- c. Change in ADA titers versus baseline ADA titer by treatment
- d. Change in ADA titers at end-point by prior insulin exposure by treatment

Figure 4. Individual ADA titers over trial duration in Trials 3001 and 3004 showed that overall, consistently in both trials, cross-reacting ADA nature seems to represent majority of the ADA titers for both treatment arms

Trail 3001 (original NDA):



Trail 3004 (resubmission):

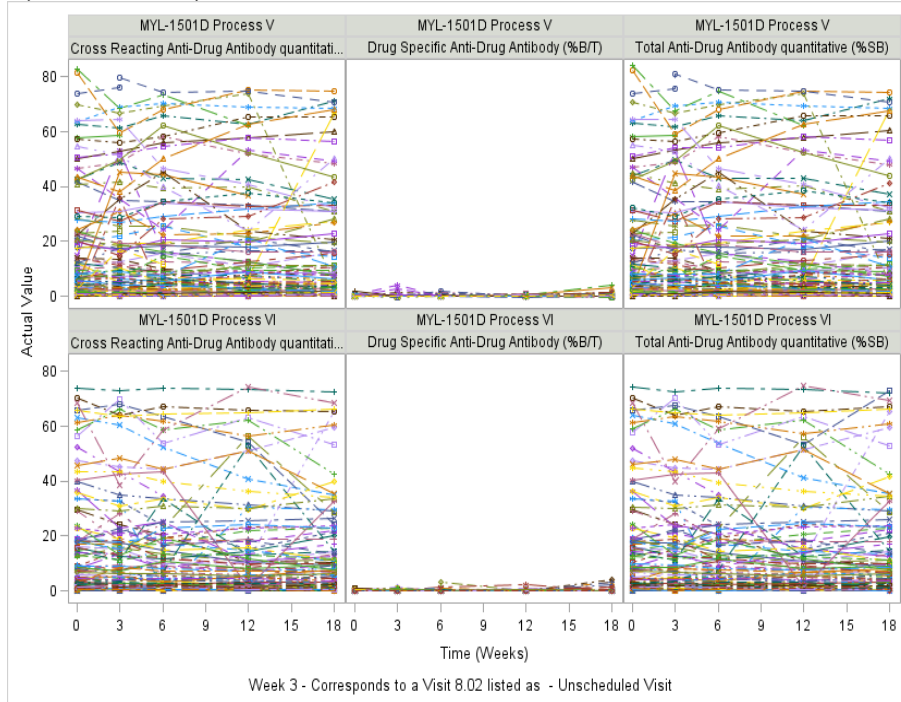
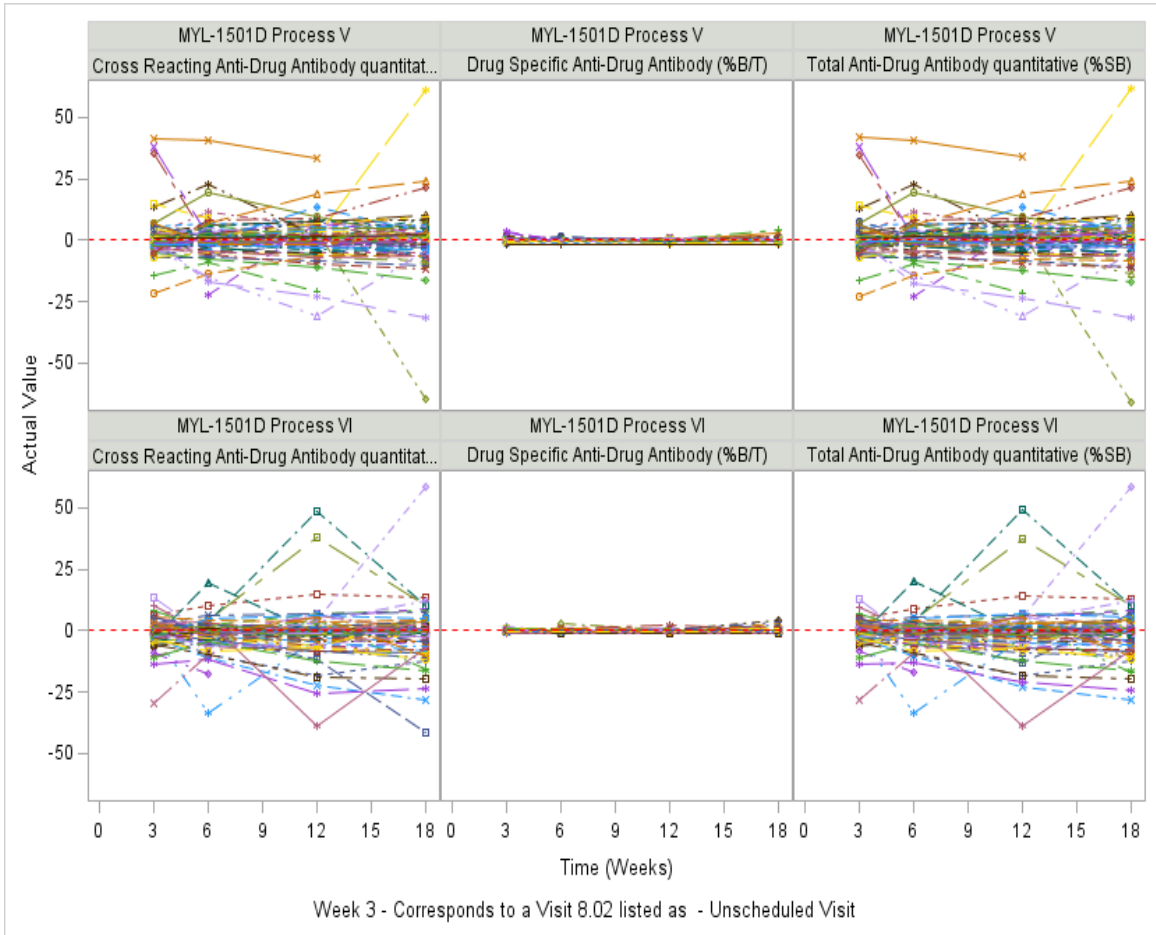


Figure 5. Individual Change in ADA Titers over trial duration in Trial 3004 showed modest change from baseline in the CR-ADA characteristics with no to minimal change in DS-ADA



Majority of subjects show minimal change in ADA titers with very minimal change in drug-specific ADA titers, which per se were relatively low. In some subjects the change in cross-reacting ADA was of transient nature.

The figure below presents the cumulative distribution function plot for change from baseline in ADA titer at end-point, and for baseline ADA titers by treatment.

Figure 6. CDF Plots for Change in ADA Titers at Week 52 (Top) and at Baseline (Bottom) in Trial 3001 [CRADAN=Cross-Reacting ADA; DSADA= Drug specific; TADAN=Total ADA]

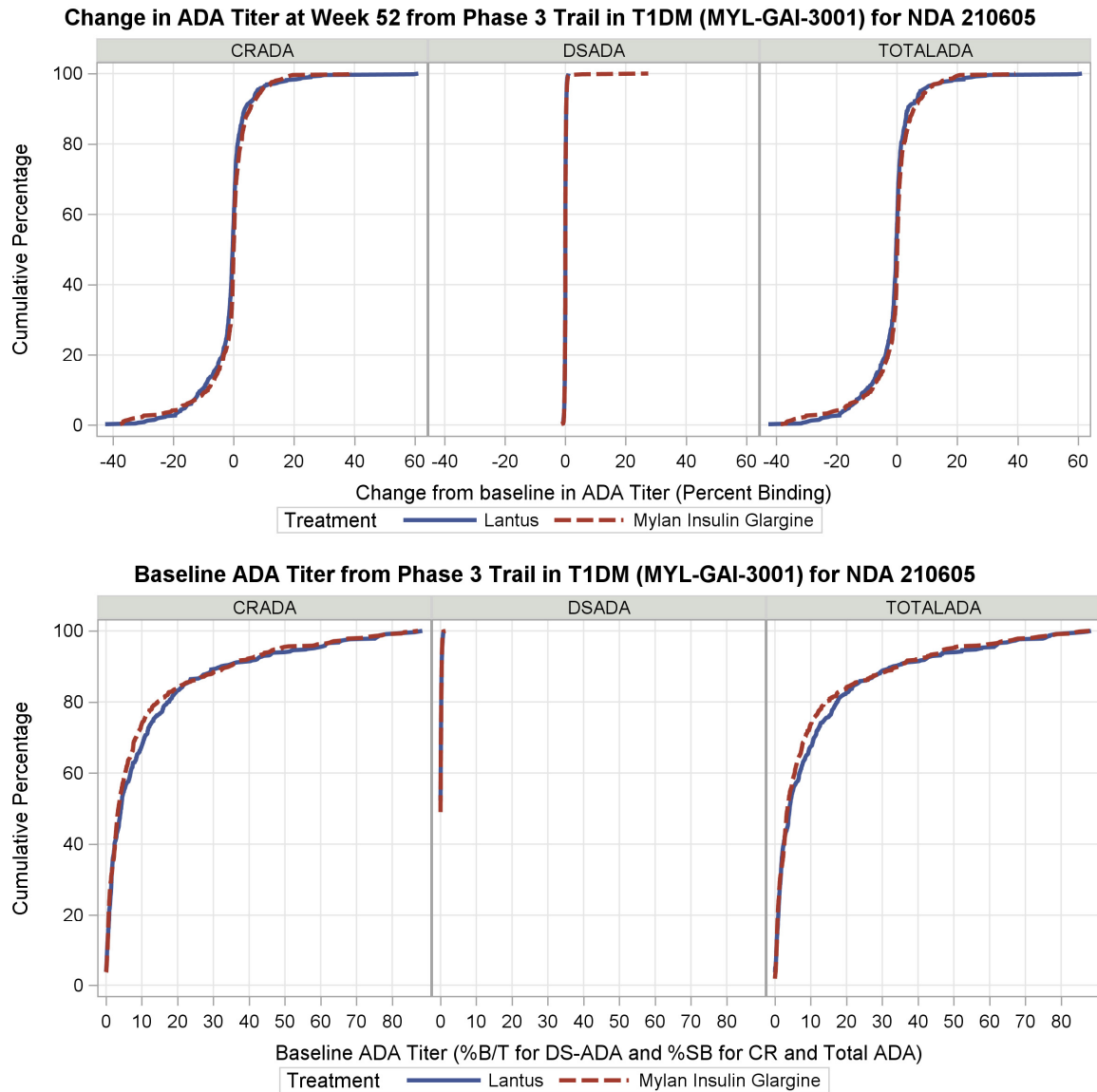
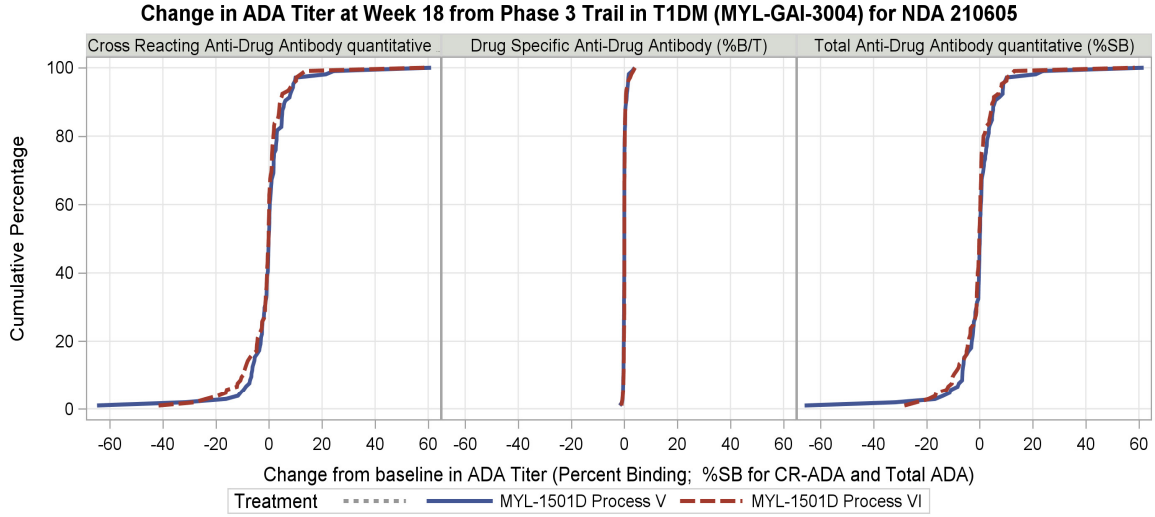
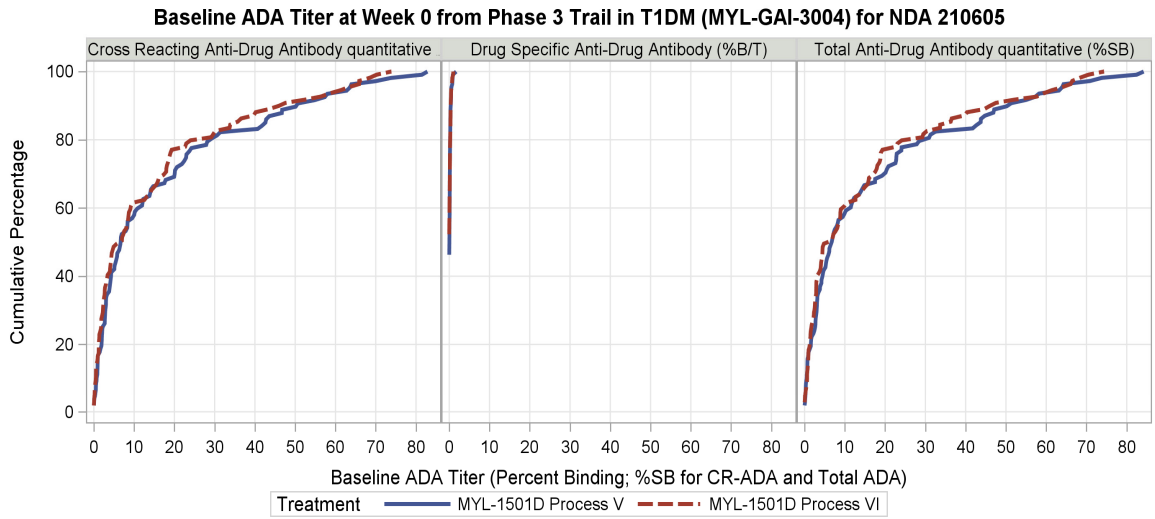


Figure 7. CDF Plots for Change in ADA Titers at Week 18 (Top) and at Baseline (Bottom) in Trial 3004 [CRADAN=Cross-Reacting ADA; DSADA= Drug specific; TADAN=Total ADA]

Week 18 Change (Trial 3004):



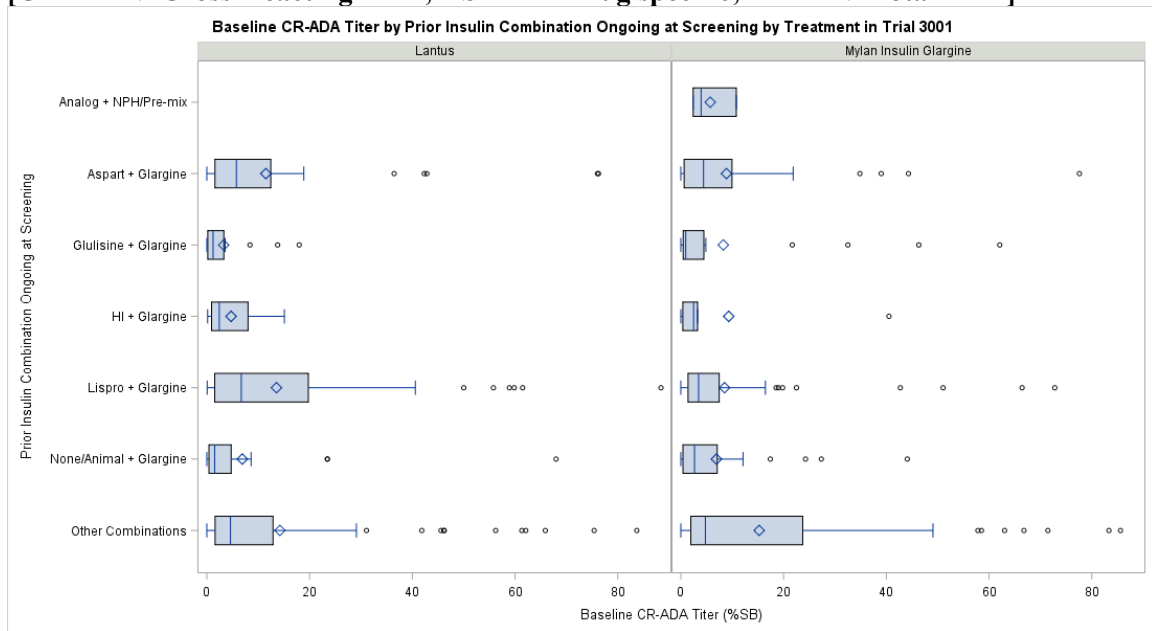
Baseline (3004):



The distribution of change from baseline in all ADA titer types overlapped between Process V and Lantus and similar trend was observed for Process VI versus Process V treatment arms with homogeneous baseline titers. Roughly 60% of subjects showed no change and almost 20% subjects each showed either rise or decline from baseline.

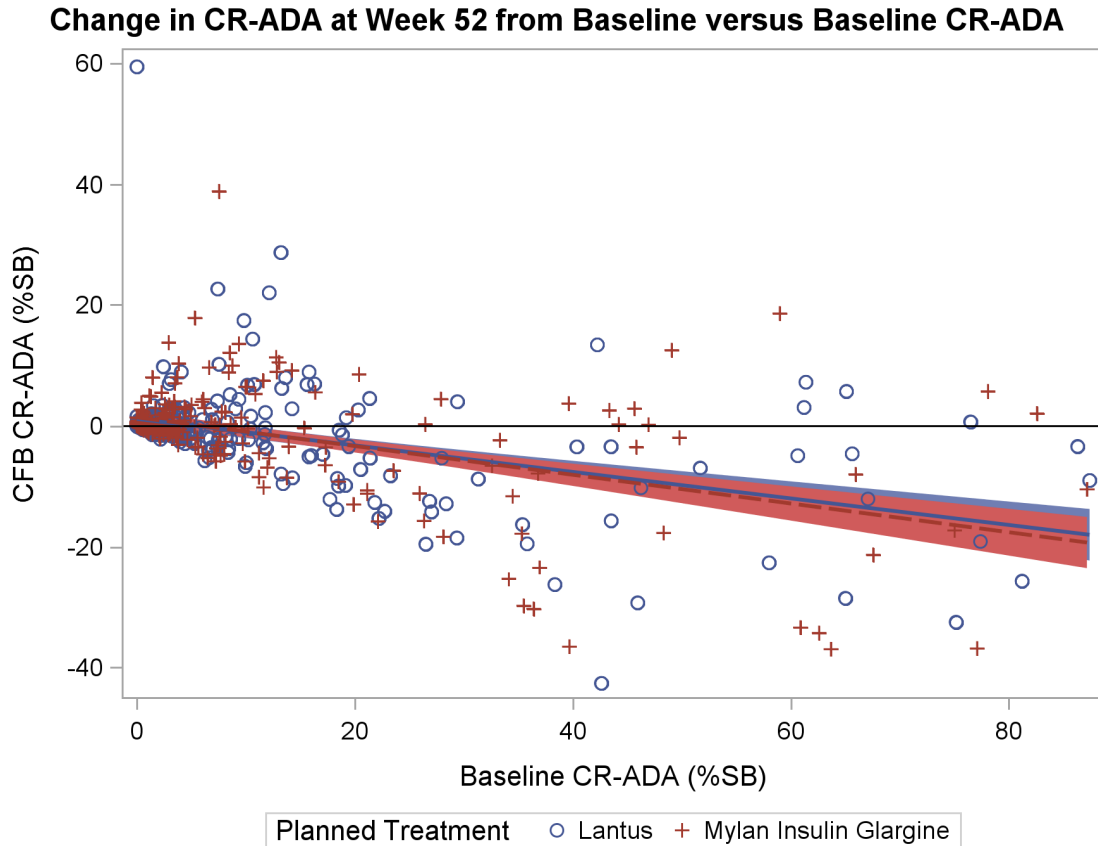
Baseline ADA distribution overlapped between the two treatments, which seems to indicate the homogeneity brought in by the randomization between two treatment arms. However, whether it is reflective of homogeneity due to the wash-out from prior insulin generated CR-ADA during the run-in phase (if 4-6 weeks are enough for that change) or homogeneity in the immune response of heterogeneous prior combinations remains to be explored further although distribution of baseline CR-ADA titer was plotted by prior insulin combination ongoing at the time of screening by treatment in Trial 3001 (Figure 8) and there is no apparent trend of difference in CR-ADA distribution between these subgroups. Though, if 4-6 weeks are enough for wash-out, the rationale for longer evaluation would be the facilitation of prospective change in ADA titer and HbA1c post-randomization.

Figure 8. Box Plots for Baseline ADA Titers by Prior Insulin Use in Trial 3004 [CRADAN=Cross-Reacting ADA; DSADA= Drug specific; TADAN=Total ADA]



Given the study design aspects of SEMGLEE clinical trials, we further assessed if the baseline ADA status influences the final ADA change over the treatment duration. The Figure 9 below presents a scatter plot looking at correlation of final change to baseline ADA for CR-ADA (being the prominent ones) in Trial 3001 (being longest duration of the two trials):

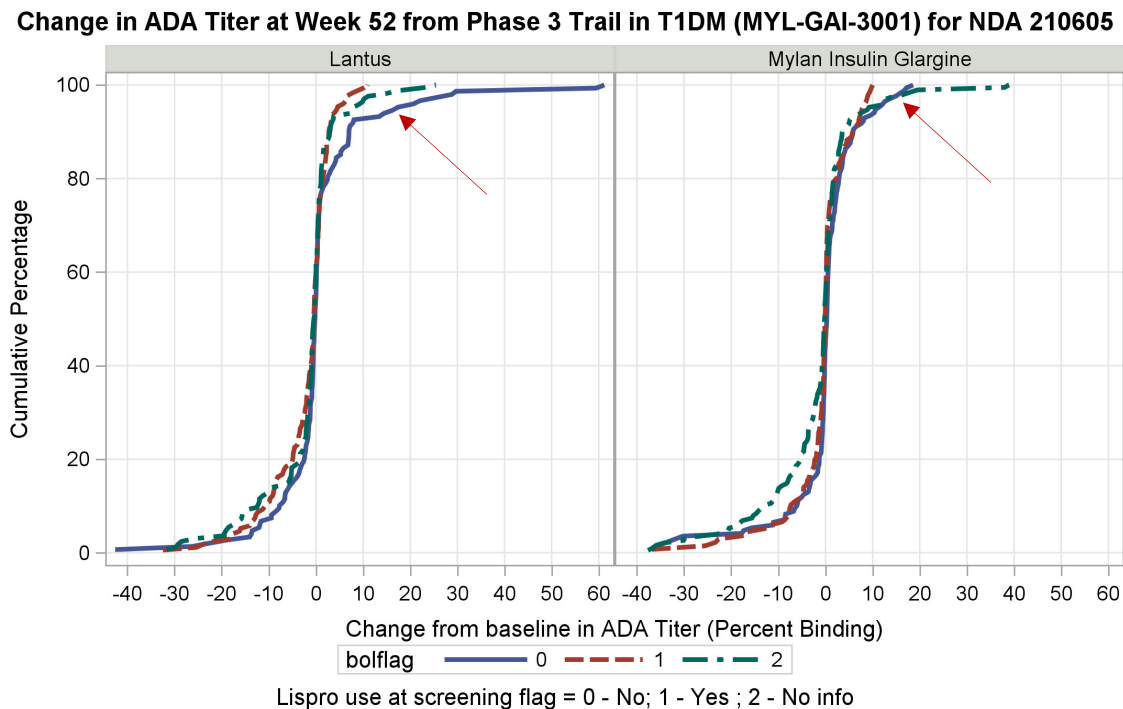
Figure 9. Change from Baseline in CR-ADA at Week 52 versus Baseline CR-ADA titers in Trial 3001



The data in general points to a trend for increase from baseline for low ADA titer subjects and vice versa consistently for both treatments. However, there is significant heterogeneity in the response data to conclusively comment on the predictability of baseline ADA status towards the final trend. Whether the presence of wide magnitude of ADA at baseline per se affects the sensitivity of trial in detecting a clinically meaningful difference remains to be explored. Though it is certain that the immune system may already be exposed to variety of insulins (or antigens) in a subject's time of insulin use (Figure 2) and at least two insulins in the trial.

Further in SEMGLEE trial 3001, subjects were also shifted with regards to their prandial insulin component – Humalog (Insulin Lispro) in this case to bring homogeneity in the prandial component across two treatment arms. Therefore, to assess whether prior insulin lispro use (despite of the run-in phase) has any influence on CR-ADA, which both insulins can generate, the cumulative distribution of change in CR-ADA was plotted by prior insulin use (Figure 10 below). Subgroups labeled as 0 – No prior insulin lispro use at screening, 1-Prior use of insulin lispro at screening, and 2-no information available in database.

Figure 10. Change from Baseline in CR-ADA at Week 52 By Prior Insulin Lispro Exposure Flag in Trial 3001



Data appears to indicate a different and relatively higher magnitude of increase in CR-ADA titer in subgroup of subjects who did not have prior exposure to Humalog (indicated by red arrows) and raised several scenarios – The trials are intended to evaluate Insulin Glargine immune response alone, and

- (i) can it be assumed that immune response from the prandial component will be absent?
- (ii) doesn't count? or
- (iii) that the immune response to insulin lispro and insulin glargine is mutually exclusive, or
- (iv) that the response of prandial component to ADA is similar in both arms given the same average unit/kg dose utilization (if there is a dose-immune response) and same product used in both arms?
- (v) If CR-ADA response is not from insulin glargine alone then how to interpret this data?

However, this observation needs further evaluation.

Nonetheless, with the evolving nature of science and technology in bio/immuno-analytics, the SEMGLEE clinical trial results offered an opportunity and additional insights to ask – is it true that immunogenicity is clinically/clinical pharmacologically irrelevant for SEMGLEE in comparison to LANTUS?

3. What are the unique aspects of impact of insulin immunogenicity on relevant clinical pharmacology/clinical measurements of glycemic control for SEMGLEE in the multi-dose injection (MDI) trials in subjects with type 1 diabetes?

The primary concern for ADA is its impact on insulin PK to expect or relate it to relevant clinical observations. For a hormone replacement therapy like insulin in T1DM, in most simple terms, any interference with PK/PD could mean a loss of glycemic control if the dose is kept the same. Alternatively, there would be an unusual dose escalation to get to the same glycemic control

compared to subjects with low or no ADA titers or decrease from baseline (looking at extreme ends of the ADA change). The following sections comment on the ADA correlation with PK, Insulin Dose, and HbA1c.

Impact of ADA on PK: The pre-dose trough insulin glargine M1 metabolite concentrations were collected in Trial 3004 and were evaluated for their correlation with Total ADA for simplicity. Both absolute and dose-normalized concentrations were plotted versus absolute ADA or change in ADA titer at each visit over the 18 Week trial duration.

There is no apparent trend of correlation of actual (Fig. 11) or dose-normalized concentrations (Fig. 12) at all visits with ADA titers except a slight upward trend with increasing titers at baseline (visit #6), with no trend apparent versus change in ADA titers at each treatment visit (Fig. 13) thus, indicating a lack of impact of ADA on M1 systemic concentrations.

Figure 11. M1 Concentration versus Total ADA by treatment and visit in Trial 3004

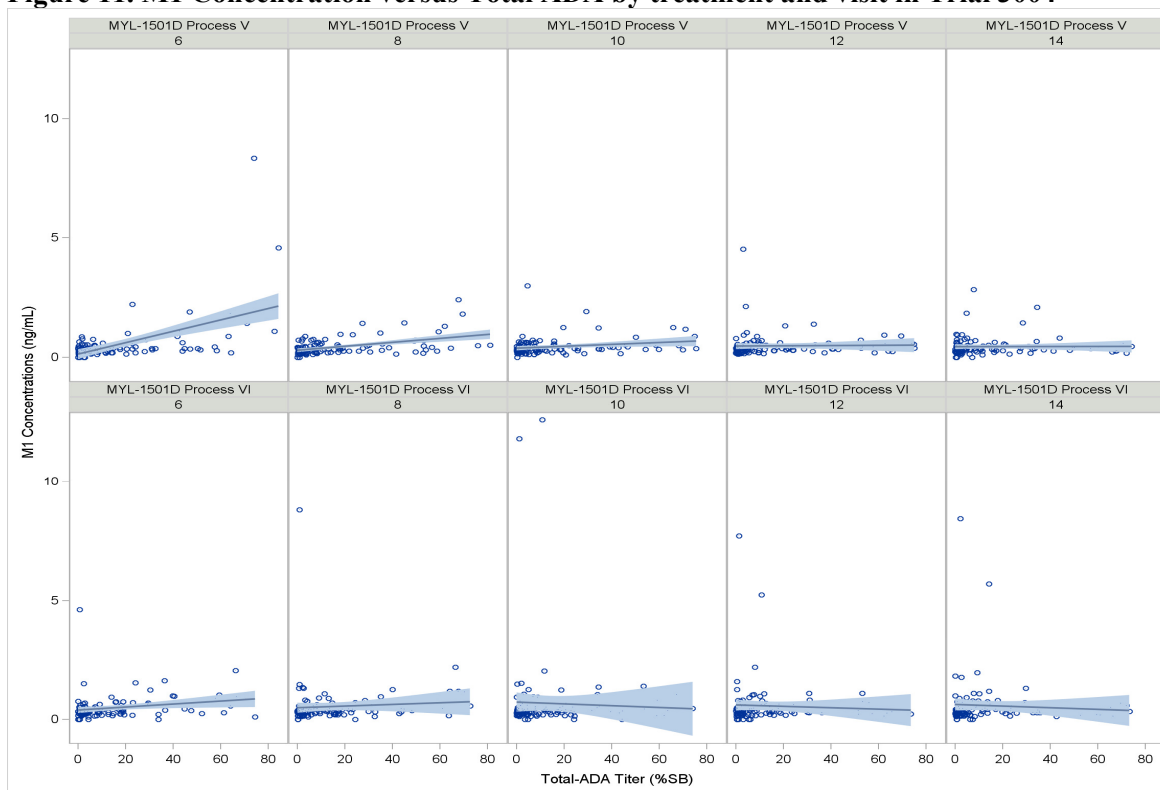


Figure 12. Basal Dose Normalized M1 Concentration versus Total ADA by treatment and visit in Trial 3004

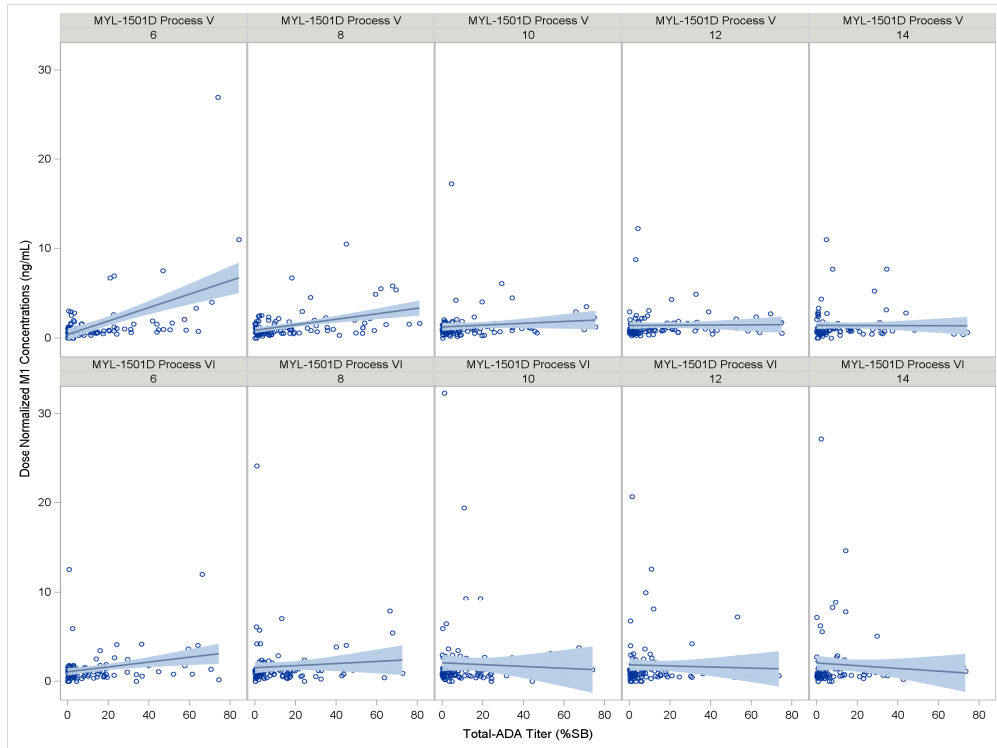
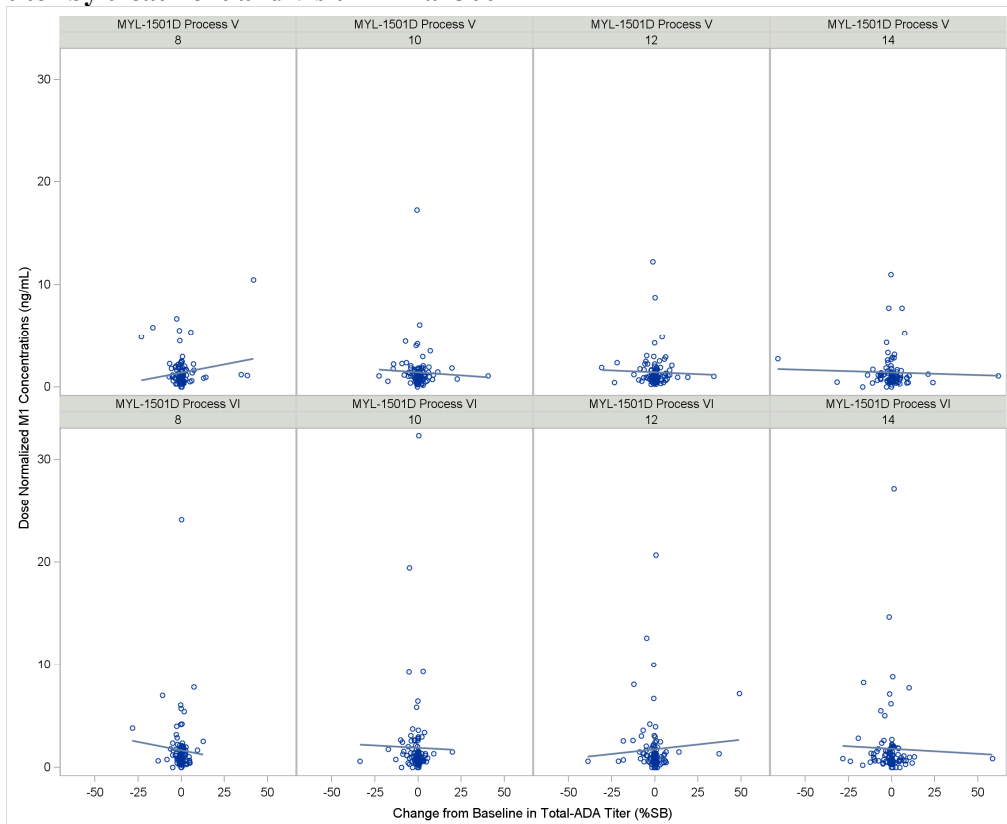


Figure 13. Basal Dose Normalized M1 Concentration versus Change from Baseline in Total ADA titer by treatment and visit in Trial 3004



Impact of ADA on Insulin Dose: Readers can refer to review by statistical and clinical reviewers for details on acceptability of the claims on the comparison of dose among treatments. Being longer of the two trials, trial 3001 results were graphically analyzed to understand the longitudinal trends in insulin dose utilization by treatment at individual level. This was done to see if there are any unusual trends of increase or decrease from baseline in the trial subjects.

Overall, from actual dose over time and change from baseline over time plots showed that the prandial, basal, and thus total insulin dose remained stable throughout the trial, with usual ups and downs corresponding to the fact that insulin is individually titrated (Fig. 14 and 15). The mean dose versus time plot (Fig. 16) further confirms this trend at population average level. This observation possibly indicates similarity in the inherent in vivo potency (dose-response) of the two insulin products under comparison if the glycemic control achieved is of the same magnitude (in the background of similar prandial dose utilization). This is a fundamental clinical pharmacology principle that is deeply embedded in insulin development and therapeutic use, and likely exists since the first insulin was approved comparing to other insulin with an established unit dose.

Figure 14. Individual Level Average Daily Insulin Dose by Treatment in Trial 3001

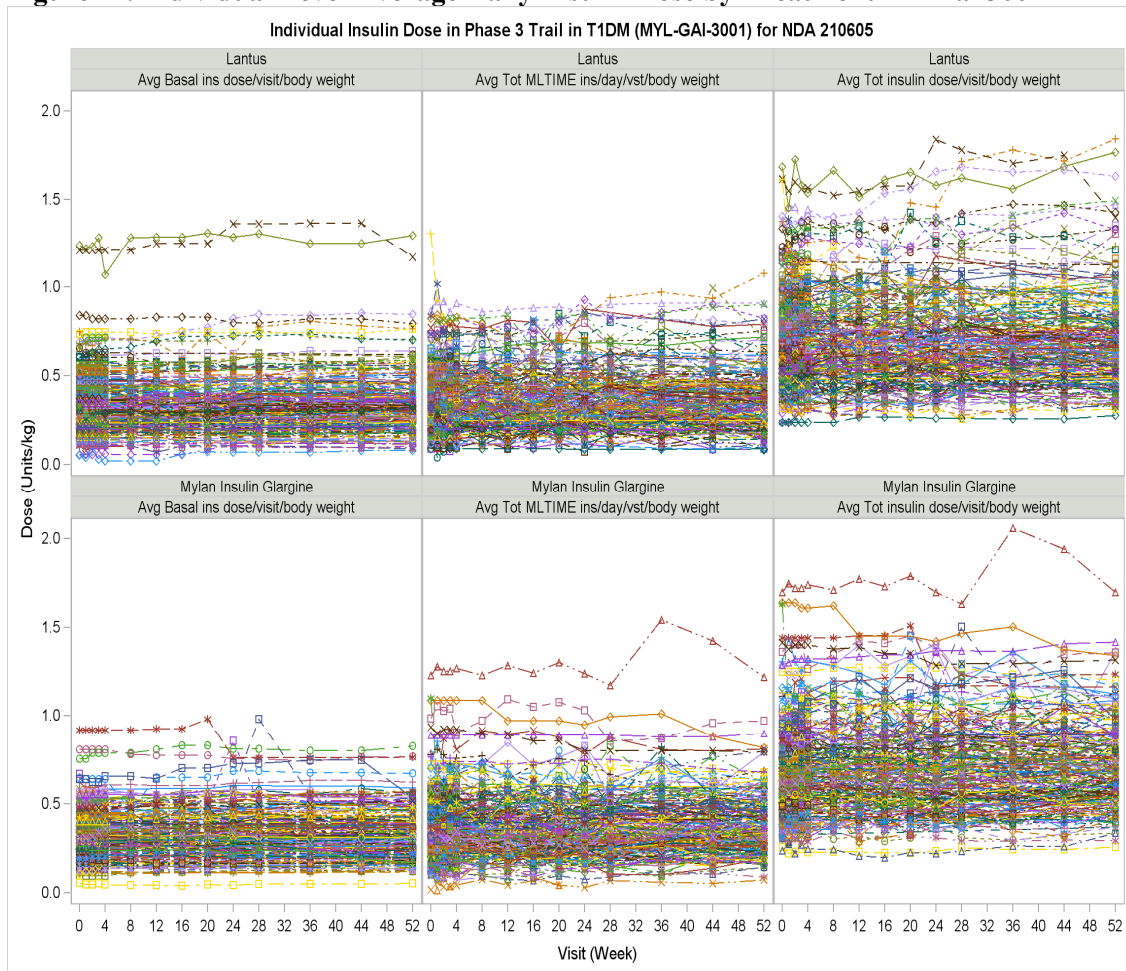


Figure 15. Individual Level CFB in Average Daily Insulin Dose by Treatment in Trial 3001

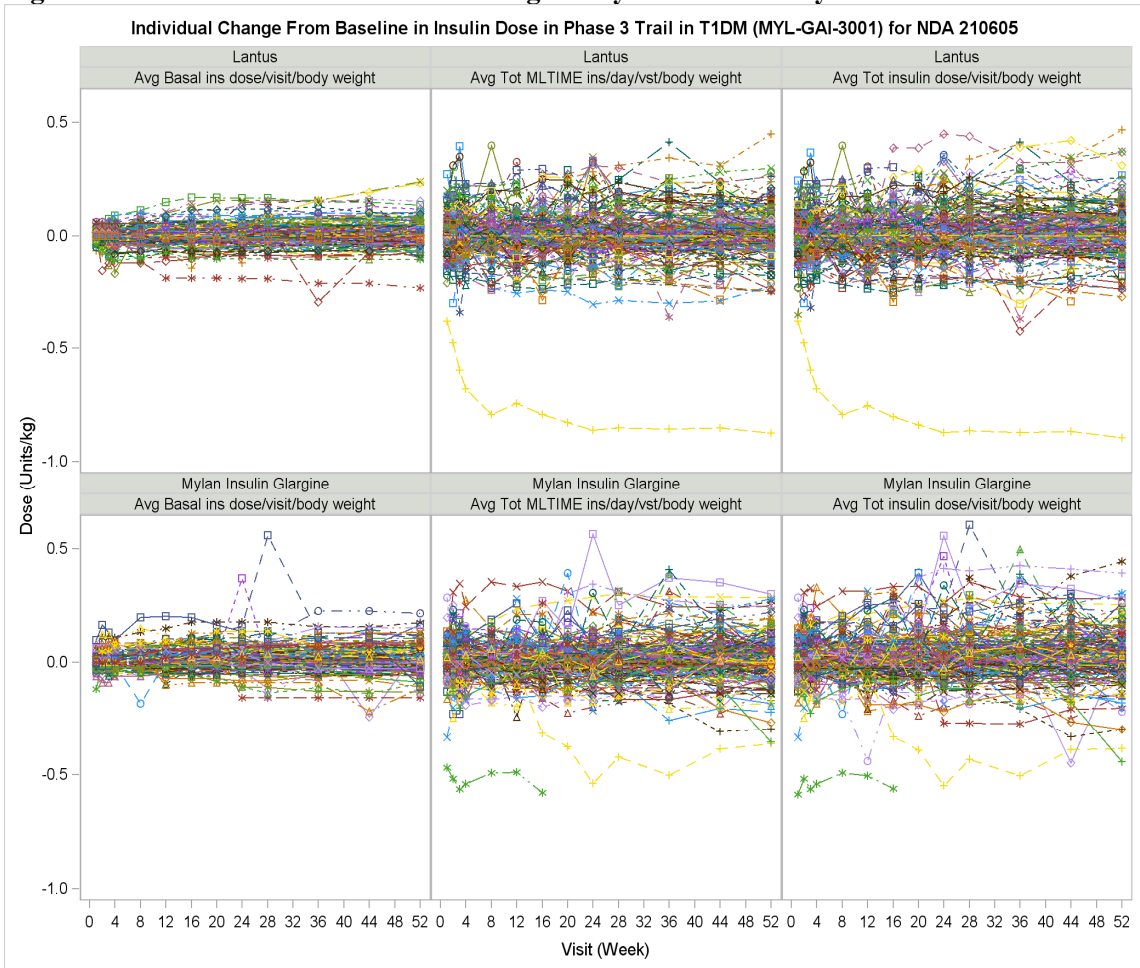
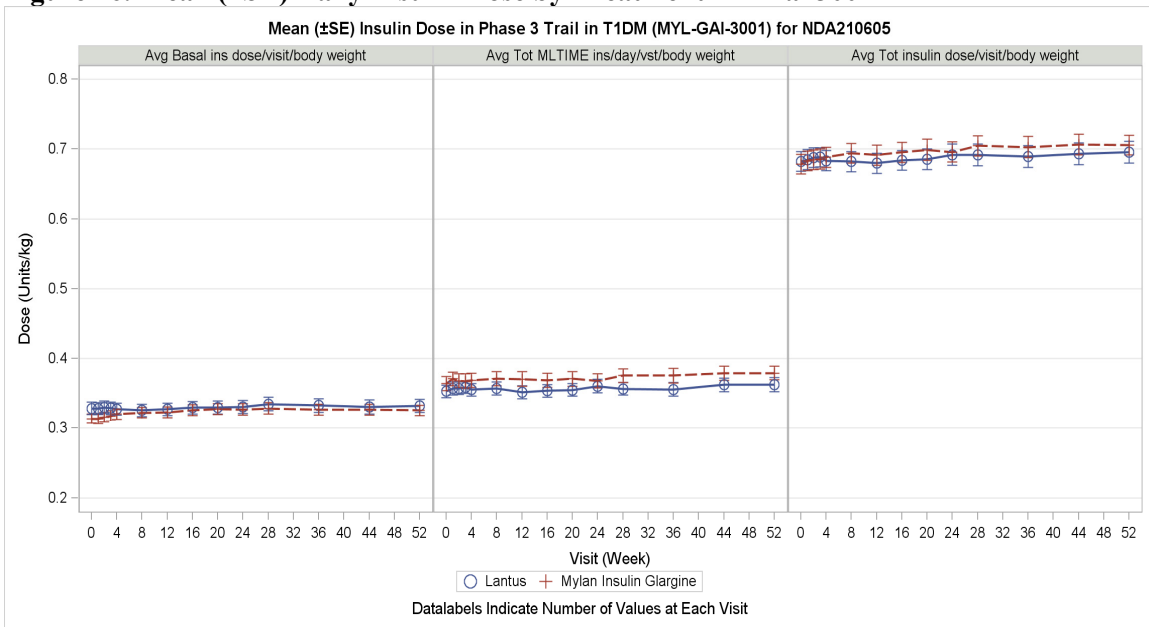


Figure 16. Mean ($\pm$ SE) Daily Insulin Dose by Treatment in Trial 3001



Prior to discussion on the impact of ADA on insulin dose utilization, it is worthwhile to consider the actual change in insulin dose happening at population average level to create a context from clinical relevance perspective. The box plot below in Figure 17 presents the change from baseline in total insulin dose by treatment. SEMGLEE and LANTUS (Prandial and Basal trends are no different).

On average the change in total insulin dose from baseline is ~0.01 unit/kg, 50% of change being within about -0.05 to 0.10 units/kg, and a decrease or increase of ~0.25 units/kg from baseline on extremes for both treatments. From a clinical pharmacology perspective this is not meaningful change based on known dose-response of insulin glargine.

Further, Figure 18 presents a scatter plot for change in dose versus change in CR-ADA titer to assess if at extremes of the changes in systemic milieu of presumed insulin binding (or neutralizing!) ADA, there is a systematic trend for change in insulin dose. There was no trend apparent for prandial, basal, and thus total insulin unit/kg dose change with CR-ADA titers consistently for both treatments.

Figure 17. Distribution of Change in Total Daily Dose at Week 52 in Trial 3001

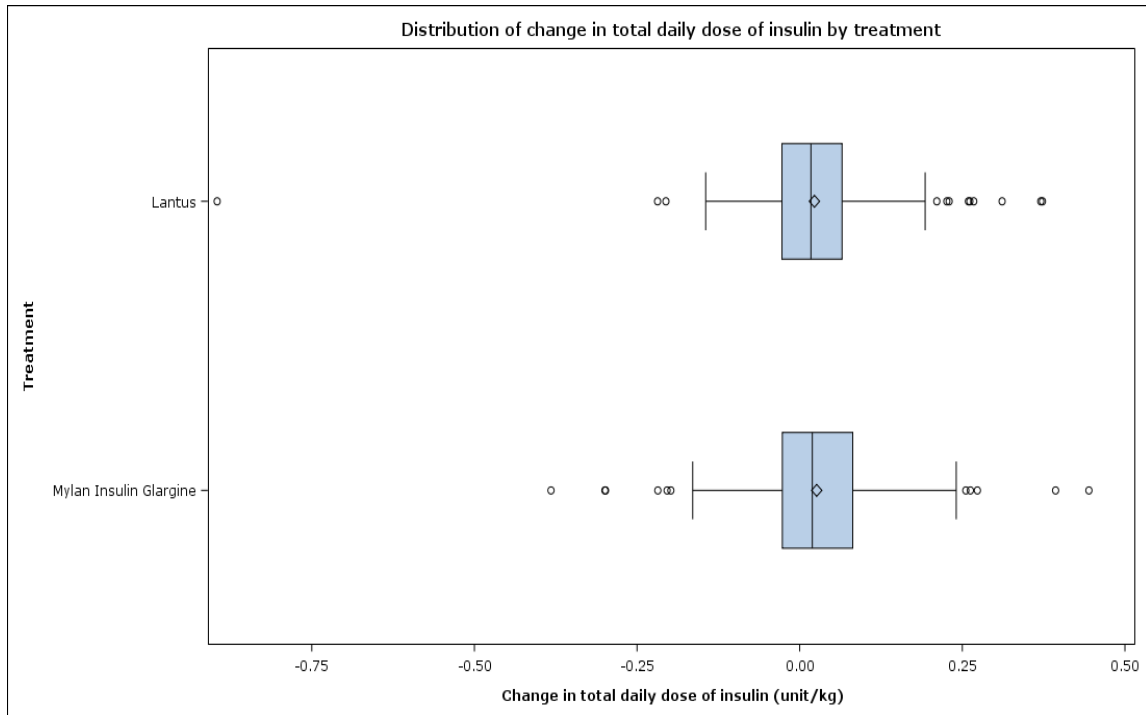


Figure 18. Change in Total Daily Dose at Week 52 versus Change in CR-ADA titers



Impact of ADA on HbA1c: Readers can refer to review by statistical and clinical reviewers for details on acceptability of the claims on the comparison of HbA1c among treatments. Trial 3001 results were graphically analyzed to understand the trends in HbA1c change by treatment. A standalone 2-dimensional analysis of dose versus ADA and HbA1c versus ADA would provide an information on impact or lack thereof of ADA titers. A multi-dimensional analysis was pursued to assess the impact of ADA-Titers on HbA1c and Dose simultaneously to assess if there was any systematic objectivity in change in the dose.

In bubble plots below each bubble represent an individual change in HbA1c in relation to the respective change in ADA Titer from baseline, while the bubble size is proportionate to change in insulin dose from baseline at week 52. Expectation is that HbA1c should increase (deterioration of glycemic control) or decrease (improved glycemic control) with changes in ADA-Titers, if e.g., dose is not adjusted (same bubble size) and ADA had any impact on the PK/PD. Consistently for both treatments in Trial 3001, the data doesn't show any trend for a relationship between HbA1c change and Change in CR-ADA titers or with actual ADA titers in the background of similar change in insulin dose across the whole spectrum of ADA titers.

Figure 16. Change in HbA1c and Dose versus Change from Baseline in ADA Titer at Week 52 in Trial 3001

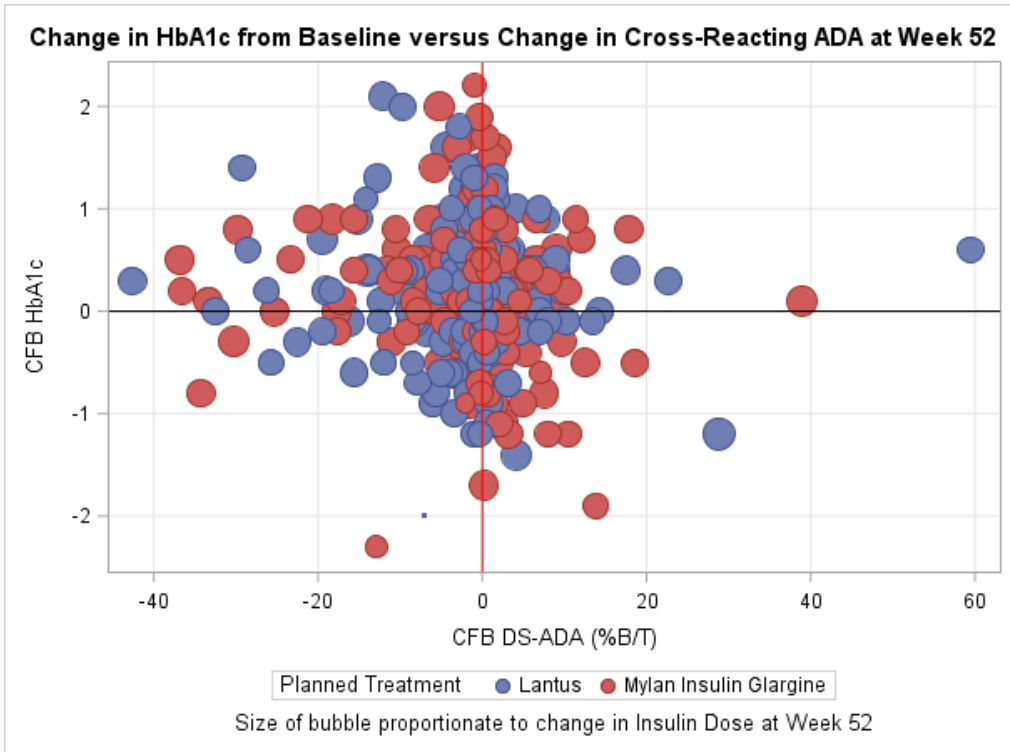
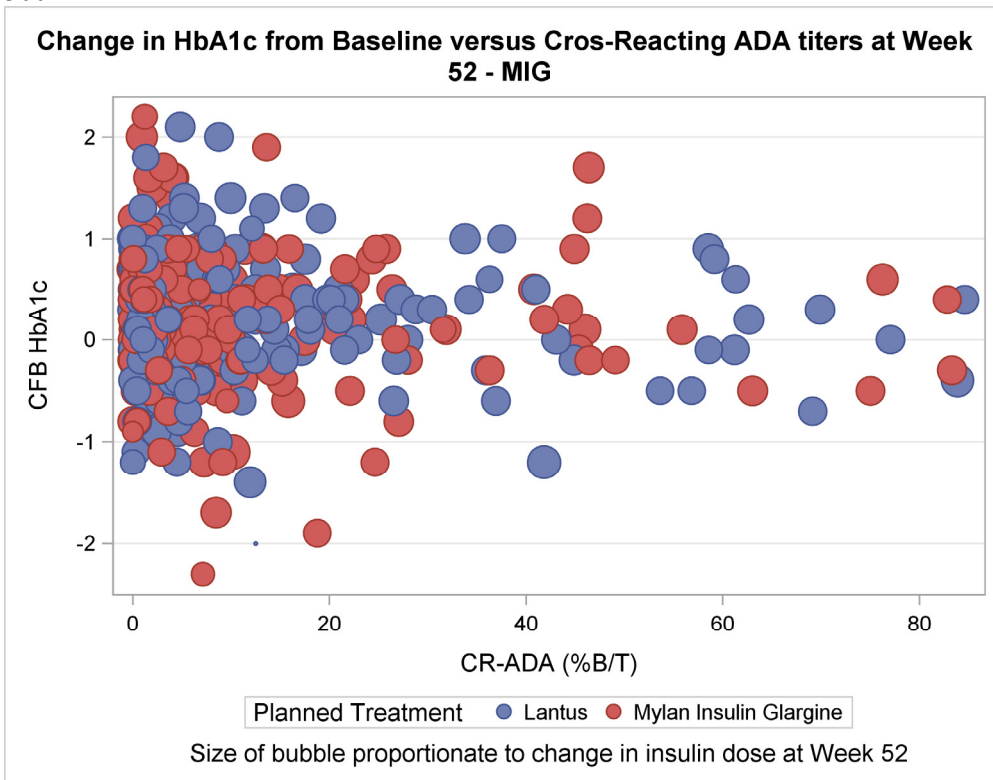


Figure 16. Change in HbA1c and Dose versus Absolute CR-ADA Titer at Week 52 in Trial 3001



4. Summary of Observations for SEMGLEE

- The clinical immunogenicity assessment/comparison of SEMGLEE and LANTUS in the combination therapy setting creates a challenge in interpretation of the immunogenicity data given most ADA titers (Both in Trial 3001 and 3004) are due to the cross-reacting antibodies (cross-reacting to human insulin and mutually interacting) for which, both prandial and basal insulins are capable to generate, upon long-term use even in mutual presence.
- The magnitude of change in ADA titers from baseline in the trial duration was more prominent for cross-reacting antibodies, while minimal change in the drug-specific antibody titers. In general, there was indication for increase in titers in subjects with low antibody titer and decrease in the titers in subjects with high baseline antibody titers. However, no strong trend was observed.
- Pre-dose Insulin glargine M1 concentrations were measured at pre-specified visits in Trial 3004. Descriptive summary of longitudinal data and correlation with ADA titer was assessed for as is concentrations, units/kg dose adjusted concentrations. Insulin glargine M1 concentrations (unadjusted or unit/kg dose adjusted) did not show any correlation with absolute or change from baseline in ADA titers.
- Neither dose nor HbA1c change showed a correlation versus ADA or ADA change (including at extreme ends) and perhaps understandable considering minimal change from baseline in ADA titers >50% trial population for 3001 or 3004.
- The availability of M1 concentration data in the trial 3004 showed the lack of effect of ADA titer on M1 concentrations over the trial duration. This is consistent with the observation of similar unit/kg dose utilization and glycemic control amidst a lack of impact of ADA on unit/kg dose and HbA1c, overall supporting the conclusion that immunogenicity is not clinically important for SEMGLEE.

5. Conclusions

Per the primary review by Dr. Jing Niu, phase 1 PK/PD studies for SEMGLEE adequately demonstrate similarity of the intended commercial (Process VI) to Lantus and comparability to Clinical Trial (3001) material (Process V) in overall pharmacokinetic and corresponding pharmacodynamic profile assuring the following at population average level:

- similar in vivo potency (i.e. glycemic reduction response/unit dose) and
- overlapping time-action profile (i.e., similar time to peak concentration/peak effect and duration of systemic exposure/response)

Collectively this may mean that one can expect no change/difference in dose and dosing frequency for SEMGLEE from LANTUS during clinical use.

The comparative data from clinical trials (3001 and 3004) on dose (basal, bolus, and total units/kg) utilization vis-à-vis similar magnitude of glycemic control (upon acceptability of claims from statistical analysis) would support that this is a reasonable expectation. Further, it shows that in the context of follow-on insulin products, like SEMGLEE, the PK/PD studies were very informative about the efficacy in a stricter dose-response sense.

Since SEMGLEE PK/PD studies were replicate cross-over design, they also showed the intra-subject variability in PK/PD was no different than for Lantus. Thus, further reassuring that among other factors known to influence the primary safety concern – hypoglycemia incidence in T1DM can be expected to be similar assuming day-to-day variability in insulin PK/PD profile has any

known implication on this safety concern. Trial 3001 data reports comparable incidence of severe hypoglycemia (Readers are further referred to the clinical review of the Trial 3001).

In retrospect, both Process VI (relatively purified) and Process V products demonstrated similar magnitude of immunogenicity change as the reference - LANTUS, with neither revealing any correlation to unit/kg dose or glycemic control measures.

Given that insulin therapy is marred by intra-subject/inter-subject variability, it is worth raising a question whether for SEMGLEE, which besides having similar PK/PD profile, have similar magnitude of intra-subject and inter-subject variability as LANTUS, is it even possible to tease out the impact of immunogenicity as a factor or co-factor, if any, on HbA1c, FPG, PPG, dose, or hypoglycemia incidence for SEMGLEE in these trials, and that too in the presence of another prandial insulin – Insulin Lispro?

Finally, a reasonable question to raise is – how informative these clinical evaluations are for SEMGLEE (including clinical trial and intended commercial version comparison), given the evidence presented in analytical comparisons, non-clinical, and Clinical Pharmacology comparisons? It may either be worth exploring the reasons or accepting the observation that immunogenicity for SEMGLEE does not have relevance on clinical outcome same as that of LANTUS.

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/

MANOJ KHURANA
08/16/2019 12:32:05 PM

CHANDRAHAS G SAHAJWALLA
08/16/2019 01:59:34 PM

CLINICAL PHARMACOLOGY REVIEW

NDA	210605 / 0045
Submission Dates	02/28/2019 (Class 2 resubmission after complete response dated 05/17/2018)
Proposed Brand Name	Semglee
Generic Name	Insulin glargine (MYL-1501D)
Reviewer	Jing Niu, M.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Mylan GmbH
Formulation; Strength; Presentation	Solution for subcutaneous injection; 100 units/mL; 10 mL vial and 3mL cartridge
Relevant IND	105279
Indication	Long-acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus

Contents

1 Executive Summary	2
1.1 Recommendations	2
1.2 Regulatory History	3
1.3 Summary of Important Clinical Pharmacology Findings	3
2 Question-Based Review	3
2.1 General Attributes	3
2.2 Key Clinical Pharmacology Questions	5
2.3 Bioanalytical	18
3 Preliminary Labeling Recommendations	22
4 Appendix	24
4.1 Synopsis of Study MYL-1501D-1004	24
4.2 Synopsis of Study MYL-1501D-1003	30

1 Executive Summary

The sponsor submitted NDA 210605 via the 505(b)(2) regulatory pathway to seek approval of subcutaneous (SC) administration of Semglee (MYL-1501D) indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. The sponsor is relying upon the Agency's previous findings of safety and effectiveness for the reference listed drug (RLD), Lantus[®] (Insulin Glargine Recombinant; NDA 021081, Sanofi Aventis US). Semglee is proposed as a 100 units/mL solution of MYL-1501D for SC injection, and will be made available in 10 mL vial presentation as well as 3 mL cartridge sealed in a prefilled pen injector.

In the original submission of NDA210605, four clinical studies were submitted, including two pharmacokinetic and pharmacodynamic (PK/PD) similarity studies (MYL-1501D-1001 and GLARGCT100111), as well as two Phase 3 efficacy and safety trials in patients with type 1 diabetes (T1DM; MYL-GAI-3001) and type 2 diabetes (T2DM; MYL-GAI-3002). To address the deficiencies outlined in the complete response letter, results from three additional clinical studies were submitted in the resubmission, including PK/PD similarity studies MYL-1501D-1004 and MYL-1501D-1003, as well as a Phase 3 trial MYL-GAI-3004 in type 1 diabetes patients. This review will focus on Study MYL-1501D-1004 and MYL-1501D-1003, as both were deemed pivotal from a clinical pharmacology perspective.

For simplicity, this review refers the following:

- MYL-1501D (Process VI) for the sponsor's insulin glargine manufactured using Process VI at a facility in Malaysia. MYL-1501D (Process VI) is the to-be-marketed insulin glargine product. Mylan requests approval of the vial and cartridge presentations of MYL-1501D (Process VI).
- MYL-1501D (Process V) for the sponsor's insulin glargine manufactured using Process V at a facility in India. MYL-1501D (Process V) is the product used in the Phase 3 studies MYL-GAI-3001 and MYL-GAI-3002.
- US-Lantus for listed drug, insulin glargine approved and marketed in the United States under NDA 021081.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the clinical pharmacology data submitted under the resubmission of NDA 210605 and has the following recommendations:

- The pivotal Study MYL-1501D-1004 results are acceptable to establish PK/PD comparability between MYL-1501D Process VI formulation in vial (with polysorbate) and MYL-1501D Process VI formulation in cartridges (without polysorbate).
- Results from Study MYL-1501D-1003 are acceptable to establish PK/PD similarity between MYL-1501D (Process VI) and US Lantus, as well as the similarity between MYL-1501D (Process V) and US Lantus for the cartridge presentation. The data also establishes PK/PD comparability between MYL-1501D (Process V) and MYL-1501D (Process VI). The findings of Study MYL-1501D-1003 are consistent with that of Study MYL-1501D-1001 in the original submission.

1.2 Regulatory History

On April 27, 2017, Mylan submitted NDA210605 via the 505(b)(2) regulatory pathway to seek approval of subcutaneous (SC) administration of Semglee (MYL-1501D) indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Semglee is proposed as a 100 units/mL solution of MYL-1501D for SC injection, and will be made available in 10 mL vial presentation as well as 3 mL cartridge sealed in a prefilled pen injector.

Two PKPD similarity studies (MYL-1501D-1001 and GLARGCT100111) were submitted and reviewed in the original submission by OCP/DCP2. OCP/DCP2 determined the submitted clinical pharmacology data in the original submission was acceptable to support the approval of NDA 210605 as it pertains to the cartridge presentation of MYL-1501D formulation, pending the resolution of clinical safety concerns arising from the change in formulation from MYL-1501D (Process V) to MYL-1501D (Process VI), and CMC assessment of the claims that MYL-1501D (Process VI) is improvised version of MYL-1501D (Process V) product from a purity perspective. Submission of the adequate bridging data between vial and cartridge presentations deemed necessary for the approval of the vial presentation. Refer to the complete response letter from the Agency (reference ID: 4264503) for a complete list of deficiencies.

To address these deficiencies, results of Study MYL-1501D-1004 were submitted to establish the PK/PD similarity between vial and cartridge presentations. Results of Study MYL-1501D-1003 was also submitted to support the PK/PD similarity between intended commercial formulation MYL-1501D (Process VI) and US-Lantus, as well as between MYL-1501D (Process V) and MYL-1501D (Process VI) for the 3 mL cartridge presentation.

1.3 Summary of Important Clinical Pharmacology Findings

Highlights of PK/PD comparisons from Study MYL-1501D-1004:

- For the comparison of MYL-1501D Process VI in vial with polysorbate to MYL-1501D Process VI in cartridges without polysorbate, Study MYL-1501D-1004 showed that the geometric mean ratios and 90% confidence interval (CI) for both primary PK ($C_{\max}$ and AUC_{0-24h}) and PD ($GIR_{\max}$ and $AUC_{GIR0-24h}$) parameters were within the prespecified goalpost of 0.80 – 1.25.

Highlights of PK/PD comparisons from Study MYL-1501D-1003:

- For the comparison of MYL-1501D (Process V) to MYL-1501D (Process VI), comparison of MYL-1501D (Process VI) to US Lantus, as well as the comparison of MYL-1501D (Process V) to US Lantus, Study MYL-1501D-1003 showed that the geometric mean ratios and 90% confidence interval (CI) for both primary PK ($C_{\max}$ and AUC_{0-24h}) and PD ($GIR_{\max}$ and $AUC_{GIR0-24h}$) parameters were within the prespecified goalpost of 0.80 – 1.25.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the formulation of the to-be-marketed MYL-1501D?

Table 1 details the formulation of the to-be-marketed MYL-1501D. As highlighted, (b) (4) 20 µg/mL polysorbate-20, was added to the product formulation of the 10 mL vial presentation. This formulation change is in line with the formulation change between vials and cartridges of the RLD, US-Lantus.

Only the cartridge presentation of MYL-1501D and US-Lantus was compared in study MYL-1501d-1001, MYL-1501d-1003, MYL-GAI-3001, MYL-GAI-3002, and MYL-GAI-3004. To support the vial presentation of MYL-1501D, which has a different composition from the cartridge, study MYL-1501d-1004 was conducted to support the bridge between vial and cartridge presentations in the resubmission.

Table 1. The to-be-marketed MYL-1501D insulin glargine solution for injection 100 units/mL

Presentation	Component	Quantity/mL	Quantity per cartridge/vial	Quality standard	Function
3 mL cartridge	Insulin glargine	100 units ²	300 units ²	In-house	Active ingredient
	m-Cresol	2.7 mg	8.1 mg	USP and Ph. Eur.	(b) (4)
	Glycerol (85% (b) (4))	20 mg	60 mg	Ph. Eur.	(b) (4)
	Zinc ¹ (b) (4) (b) (4)	30 µg	90 µg	USP and Ph. Eur.	(b) (4)
	Hydrochloric acid	q.s.	q.s.	USP and Ph. Eur.	pH adjustment
	Sodium hydroxide	q.s.	q.s.	USP and Ph. Eur.	pH adjustment
	Water for injection	q.s. to 1 mL	q.s. to 3 mL	USP and Ph. Eur.	(b) (4)
10 mL vial	Insulin glargine	100 units ²	1000 units ²	In-house	Active ingredient
	m-Cresol	2.7 mg	27 mg	USP and Ph. Eur.	(b) (4)
	Glycerol (85% (b) (4))	20 mg	200 mg	Ph. Eur.	(b) (4)
	Zinc ¹ (b) (4) (b) (4)	30 µg	300 µg	USP and Ph. Eur.	(b) (4)
	Polysorbate-20	20 µg	200 µg	USP and Ph. Eur.	(b) (4)
	Hydrochloric acid	q.s.	q.s.	USP and Ph. Eur.	pH adjustment
	Sodium hydroxide	q.s.	q.s.	USP and Ph. Eur.	pH adjustment
	Water for injection	q.s. to 1 mL	q.s. to 10 mL	USP and Ph. Eur.	(b) (4)
Ph. Eur: European Pharmacopoeia; q.s.: quantity sufficient; USP: United States Pharmacopeia.					

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

²100 units of insulin glargine corresponds to 3.64 mg of insulin glargine

Source: Adjusted from Sponsor's Quality Overall Summary – Table 2.3.P/1.

2.2 Key Clinical Pharmacology Questions

2.2.1 What are the design features and main findings of Study MYL-1501D-1004?

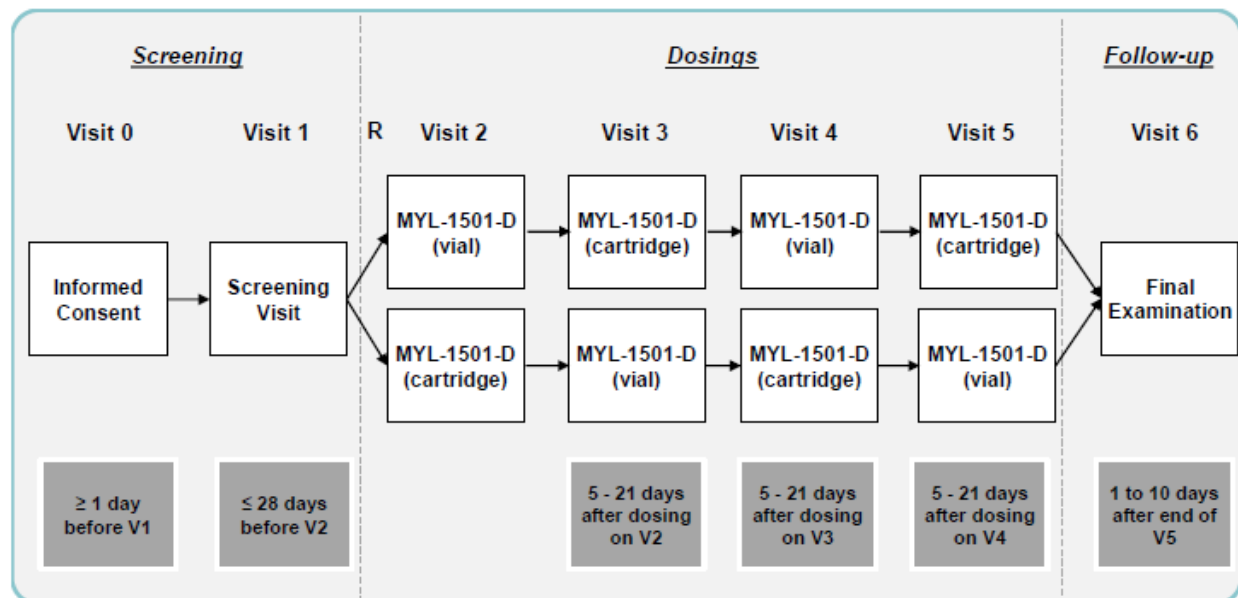
Study MYL-1501D-1004 was a Phase 1, two-center, randomized, double-blind, 4-way crossover, fully replicated, 2-treatment trial comparing single doses of MYL-1501D Process VI in vial with polysorbate with MYL-1501D Process VI in cartridges without polysorbate in healthy subjects.

In total 48 subjects (20 at trial site Neuss and 28 at trial site Mainz) were randomized to one of the 2 treatment sequences and 45 completed the trial. Three (3) subjects (6.3%) prematurely discontinued trial participation after randomization and at least 1 dose administration, all on own initiative. Each completer participated in 7 visits (Figure 1): an informed consent visit (at least one day before Visit 1), a screening visit (Visit 1, 1 to 28 days before Visit 2) to check eligibility for participation, 4 dosing visits (Visits 2, 3, 4 and 5, separated by a washout period of 5 to 21 days), and a follow-up visit with final examination (Visit 6, 1 to 10 days after Visit 5).

At Visits 2, 3, 4 and 5, the 2 insulin products were administered in 2 randomly allocated sequences in the setting of a 24-hour computer-controlled euglycemic glucose clamp (glucose clamp target: 81 mg/dL). During the clamp procedure, blood was collected pre-dose and at pre-specified intervals until 24 hours post-dose for measurement of blood glucose (for verifying ClampArt measurements) and insulin glargine metabolite - M1 (M1 is the primary circulating moiety). Safety assessments included vital signs recording, electrocardiograms (ECGs), laboratory safety parameters, physical examination, and recording of adverse events (AEs).

Overall, Study MYL-1501D-1004's design was acceptable.

Figure 1. Schematic overview of the chronological structure of Study MYL-1501D-1004



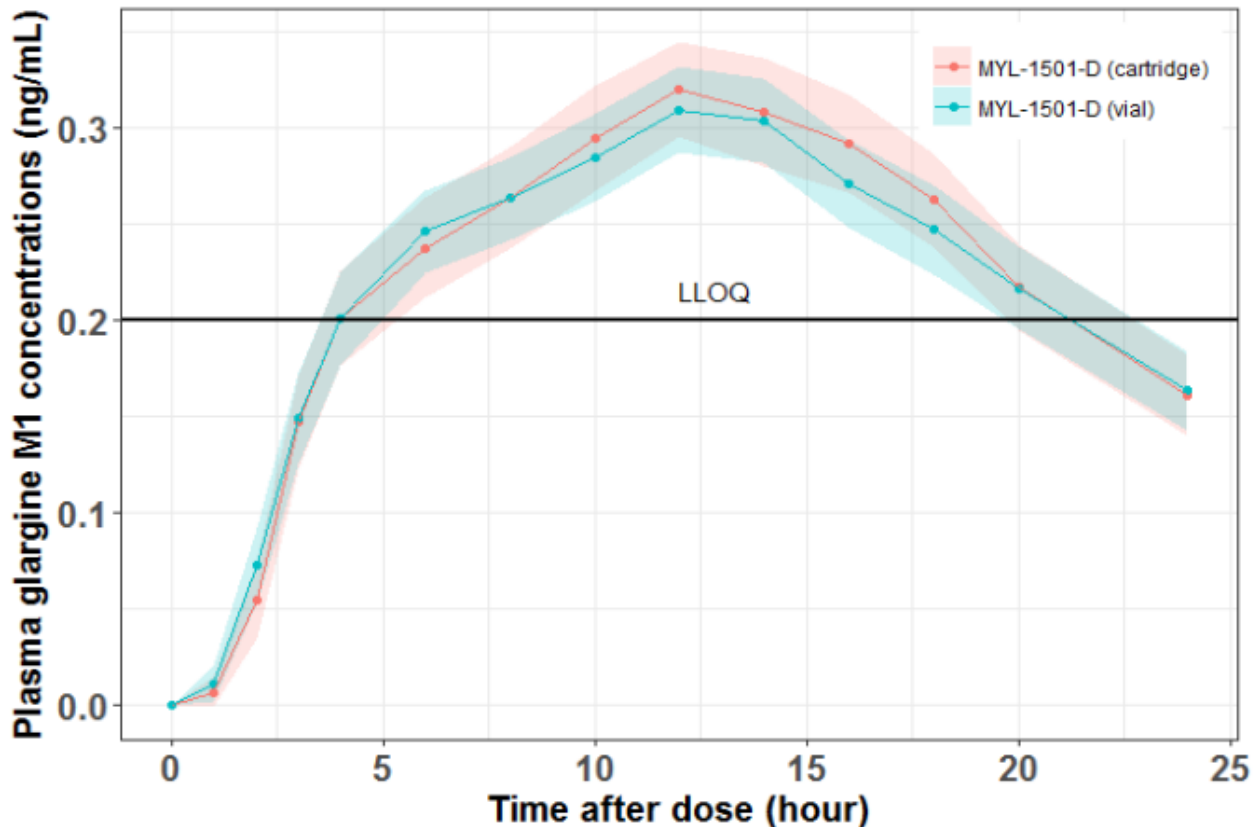
Source: Figure 1 of CSR MYL-1501D-1004

For the primary PK parameters (AUC_{0-24h} and C_{max} of insulin glargine metabolite M1), the equivalence criterion (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in both comparisons (Table 2-Table 3). Also for all secondary AUC parameters, the 90% CI of the ratio test/reference lay within these limits (Table 3).

Figure 2 shows the mean (90% CI) plasma insulin glargine concentration versus time profiles of single doses of the two MYL-1501D formulations in healthy volunteers. Upon SC injection of 0.5 unit/kg, maximum plasma insulin glargine concentrations occurred at about 12 hours post-dose for the two MYL-1501D formulations and then decline to about 20 hours near quantitation limit. In general, the mean plasma insulin glargine concentration versus time profiles of the two MYL-1501D formulations appear similar.

For the primary PK parameters (AUC_{0-24h} and C_{max} of insulin glargine metabolite M1), the equivalence criterion (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in both comparisons (Table 2-Table 3). Also for all secondary AUC parameters, the 90% CI of the ratio test/reference lay within these limits (Table 3).

Figure 2. Mean (90% CI) plasma M1 concentration versus time profiles following single 0.5 unit/kg SC doses of the two MYL-1501D formulations in Study MYL-1501D-1004. The LLOQ of 0.2 ng/mL was shown as a solid line.



Source: Reviewer's analysis

Table 2. Summary statistics of primary PK parameters in Study MYL-1501D-1004.

Statistics	MYL-1501D (vial)		MYL-1501D (cartridge)	
	AUC ₀₋₂₄ (h*ng/mL)	C _{max} (ng/mL)	AUC ₀₋₂₄ (h*ng/mL)	C _{max} (ng/mL)
N Obs	70	70	72	72
Mean	6.237	0.391	6.384	0.404
SD	1.722	0.089	1.979	0.109
CV%	27.607	22.648	30.997	27.094
Min	2.919	0.243	3.242	0.234
Median	6.017	0.375	6.290	0.386
Max	11.712	0.676	14.097	0.869
Geomean	5.997	0.382	6.091	0.390
GeoCV%	29.376	21.974	31.863	26.202

Source: Table 7 of CSR MYL-1501D-1004

Table 3. Treatment comparisons of PK parameters in Study MYL-1501D-1004

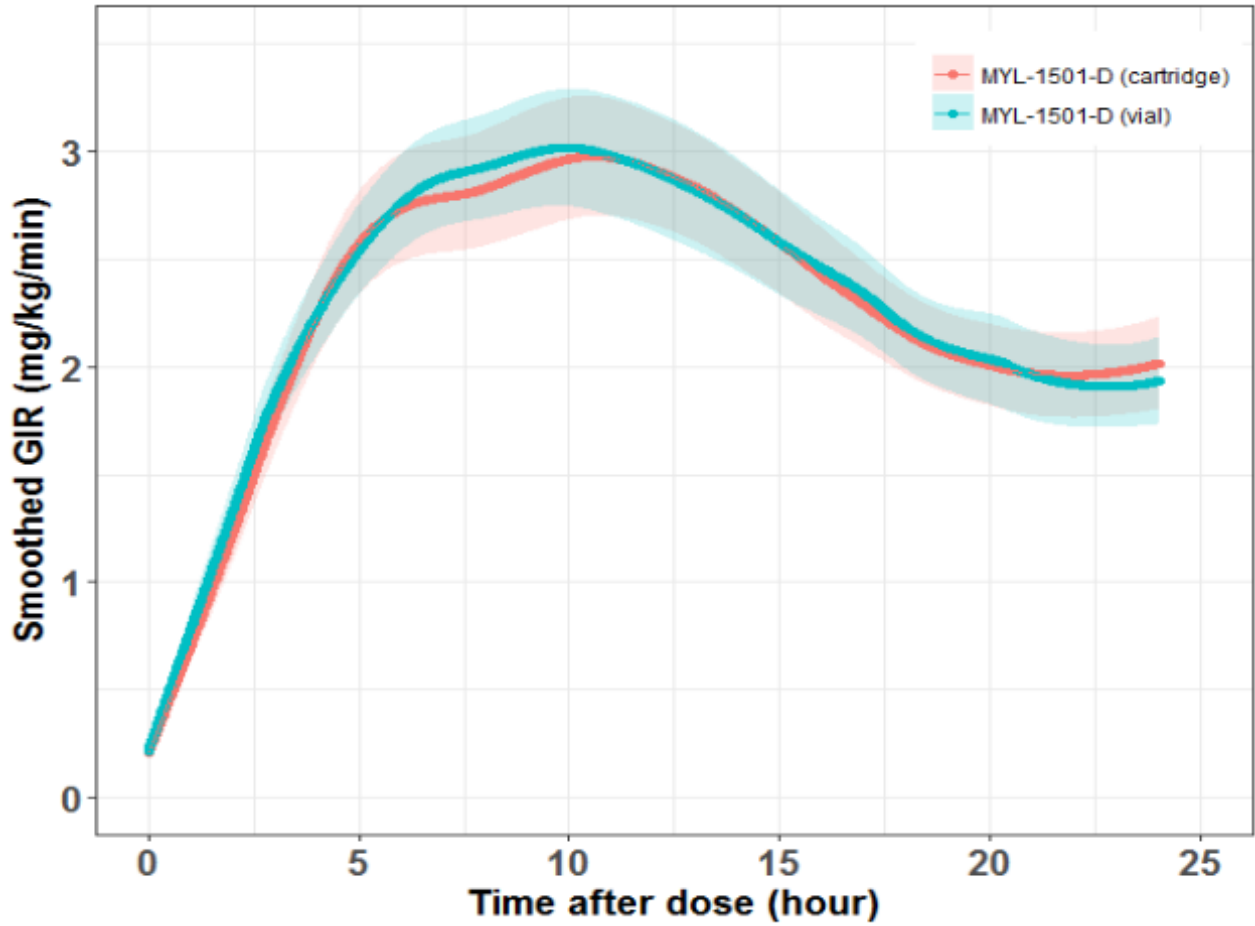
Parameter	Comparison	N Obs Vial/Cartridge	Geometric LS-mean ratio %	90% CI
AUC _{0-24h}	MYL-1501D vial vs. cartridge	70/72	97.82	(90.33; 105.94)
C _{max}		70/72	97.80	(91.55; 104.48)
AUC _{0-12h}		70/73	99.57	(90.26; 109.84)
AUC _{12-24h}		70/72	97.31	(88.95; 106.46)
AUC _{0-inf}		43/42	104.91	(95.47;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

Source: adjusted from Table 8 and Table 11 of CSR MYL-1501D-1004

Likewise, the mean smoothed GIR versus time profiles appear similar between MYL-1501D Process VI in vial (with polysorbate) and MYL-1501D Process VI in cartridges (without polysorbate) (Figure 3).

For the primary PD parameters (AUCGIR_{0-24h} and GIR_{max}), the equivalence criterion (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in both comparisons (Table 4-Table 5). Also for all secondary AUCGIR parameters, the 90% CI of the ratio test/reference lay within these limits (Table 5).

Figure 3. Mean (90% CI) smoothed GIR versus time profiles following single 0.5 unit/kg SC doses of the two MYL-1501D formulations in Study MYL-1501D-1004.



Source: Reviewer’s analysis

Table 4. Summary statistics of primary PD endpoint in Study MYL-1501D-1004.

Parameter	Treatment	N Obs	Mean	SD	CV(%)	Min	Median	Max	GeoMean	GeoCV(%)
AUC _{GIR,0-24h} [mg/kg]	MYL-1501D (vial)	90	54.592	26.6264	48.8	14.13	51.094	134.62	48.329	54.4
	MYL-1501D (cartridge)	90	54.757	26.5083	48.4	11.04	49.674	129.97	48.385	55.4
GIR _{max} [mg/kg/min]	MYL-1501D (vial)	90	3.486	1.7309	49.7	1.26	3.157	10.22	3.118	50.0
	MYL-1501D (cartridge)	90	3.520	1.6958	48.2	0.75	3.281	9.30	3.134	52.6

Source: Table 12 of CSR MYL-1501D-1004

Table 5. 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: adjusted from Table 13 and Table 15 of CSR MYL-1501D-1004

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

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

In general, the individual clamp blood glucose profiles were maintained within $\pm 15\%$ of the targeted clamp level with no obvious deviation.

Per the statistical analysis plan sponsor had the following prespecified criteria for inclusion/exclusion of subjects in the PK/PD parameter assessment and statistical analysis of the primary PK and PD parameters:

PK Analysis:

- Dosing periods of subjects who do not provide evaluable PK data for this period will be excluded from the per-protocol population (PPP) for PK according to the following reasons:
 - Less than 50% of concentration (7 measurements) above LLOQ post dosing
 - Baseline concentrations are $> 5\%$ of C_{max}

PD Analysis (Exclusion of Low-Responders):

- Dosing periods of subjects with lack of any PD response or only very low PD response for this period will be excluded from the PPP for evaluation of primary PD parameters. These subjects may be included in a sensitivity analysis.
- A subject is considered to have a very low PD response if the AUC_{GIR,0-24h} is less than 5% of the observed geometric mean AUC of respective treatment without the no responder(s) or low responder(s).

Statistical Analysis of PK and PD data:

- For statistical analysis, subjects who do not provide evaluable data for both treatments will not be included in the corresponding PPP.
- Subject profiles that do not meet clamp quality criteria will be excluded from the PPP for PD analysis.

The 45 completers of the trial were included in the PD analysis. However, 5 subjects were excluded due to the PK exclusion rules outlined in the protocol for not having data from both treatments to allow for a comparison, this led to a total of 40 subjects in the PK analysis.

Among the 40 subjects included in the PK analysis (ideally expected to generate 80 PK observations per treatment due to fully replicated design), a total of 70 and 72 PK profiles for vial and cartridge treatments, respectively, were included in the statistical analysis of primary PK parameters (AUC_{0-24} and C_{max}) due to each of the 40 subjects having at least having 1 observation per treatment. There were 18 subjects out of 40 subjects with PK data missing at 1 period of the replicate periods for the two treatments. These profiles were excluded from PK parameter assessment due to pre-defined criteria in the protocol as “Less than 50% of concentration (7 measurements) above LLOQ post dosing”.

The number of PK profiles excluded was balanced for both treatments (10 and 8 PK profiles excluded for vial and cartridges, respectively). PD data from all 45 subjects was available for analysis. The statistical analysis of both PK and PD data met the prespecified statistical criteria for PK and PD comparability (GMR and 90% CI within 80-125%). A sensitivity analysis was conducted by the reviewer by excluding corresponding PD observations for the primary PD endpoint ($AUC_{GIR0-24h}$ and GIR_{max}) and the results did not deviate from the pre-specified criteria (GMR and 90% CI within 80-125%) for PD comparability. The study perhaps was appropriately powered to handle such situations though this is unusually high number of un-usable PK profiles considering the other PK/PD studies submitted by the applicant.

The issue of acceptability of the study amidst the unusually high number of PK profile exclusion in Study MYL-1501D-1004 was discussed internally with Senior Leadership Team within the OCP. Overall there was general consensus with the review team’s conclusion on accepting the study results towards the demonstration of PKPD comparability. This was supported by the balance in number of exclusions/treatment and including support from the corresponding PD comparability data available from all subjects. Rather than an issue or substantially lower absorption, for these PK profiles it is likely that M1 concentrations were too close or lower than the LLOQ of a relatively less sensitive analytical method utilized by the applicant for this study.

Please also refer to section 2.3 of this review for additional comments regarding the high PK profile exclusion in Study MYL-1501D-1004.

In summary, Study MYL-1501D-1004 showed the PK and PD data are comparable between MYL-1501D Process VI in vial (with polysorbate) and MYL-1501D Process VI in cartridges (without polysorbate).

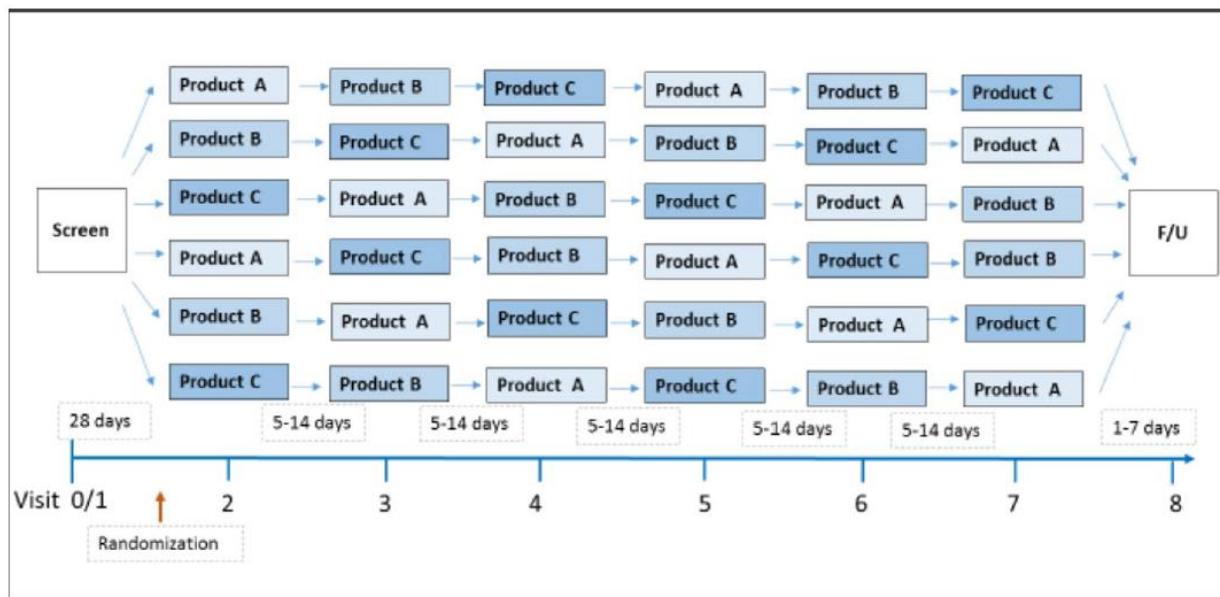
2.2.2 What are the design features and main findings of Study MYL-1501D-1003?

Study MYL-1501D-1003 was a Phase 1 randomized, double-blind, single-dose, three-treatment, six period, six sequence, fully replicated, euglycemic glucose clamp study in healthy subjects. The PK and PD of MYL-1501D produced using two different manufacturing processes (Process V and Process VI) were compared to US Lantus. The study consisted of eight study visits (Figure 4): a Screening Visit (Visit 1), six Dosing Periods (Visits 2-7) during the Treatment Period, and a Follow-up Visit (Visit 8).

There was a 5-14-day Washout Period between each of the Dosing Periods. Each Dosing Period included one euglycemic glucose clamp and was identical in procedure. PK, PD, and safety endpoints were assessed. The clamp setting was based on an automated glucose clamp technique with continuous blood glucose measurements (GlucoScout™, International Biomedical, TX) and adaptations of GIRs.

Overall, Study MYL-1501D-1003's design was acceptable.

Figure 4. Schematic overview of the chronological structure of Study MYL-1501D-1003



Product A: MYL-1501D (Process V).

Product B: MYL-1501D (Process VI).

Product C: US Lantus (insulin glargine injection) (reference).

Source: Figure 1 of CSR MYL-1501D-1003

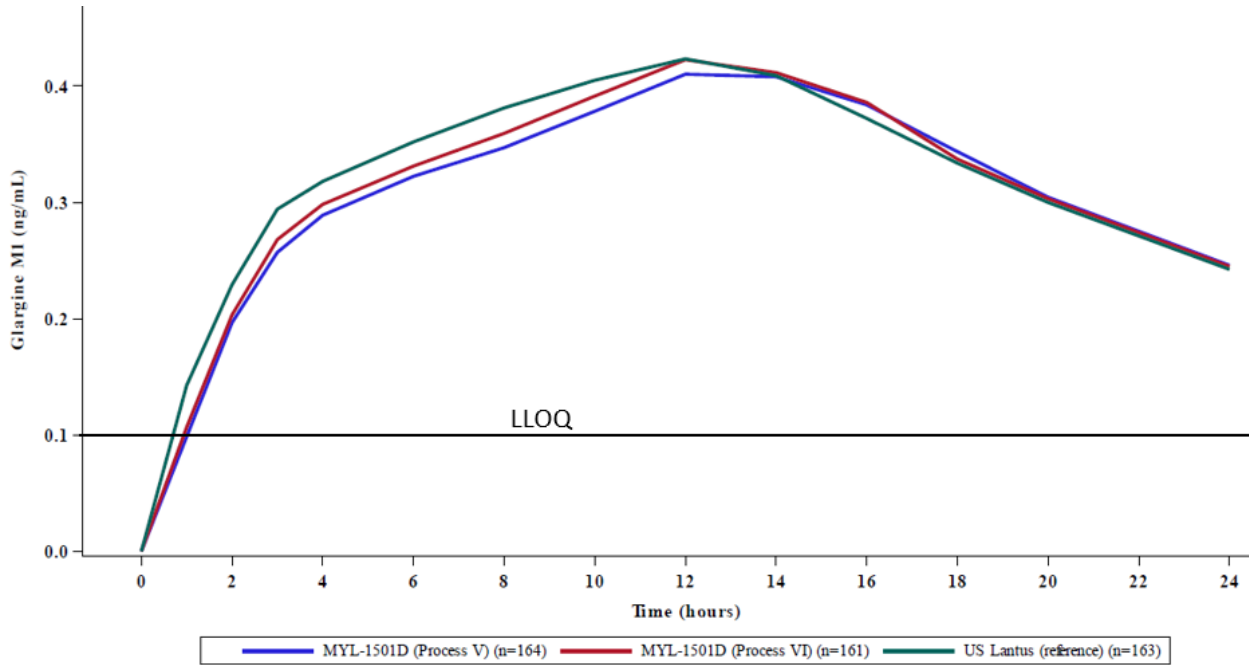
A total of 95 subjects were randomized, and 74 subjects (77.9%) completed the study. Seven subjects out of the 95 subjects were excluded from the PKPD analysis, the remaining 88 subjects, which included all subjects who completed at least 2 periods of the study without any major protocol deviation, were included in the PK analysis set. One additional subject (b) (6) was excluded from the PD analysis set as the overall mean clamp CV was 10%. Specific periods were excluded from PK or PD analysis once the periods could not meet the pre-defined requirements in the protocol.

The mean PK and PD profiles appear similar among MYL-1501D (Process VI), MYL-1501D (Process V) and US-Lantus (Figure 5-Figure 6).

For the primary PK parameters (AUC_{0-24h} and C_{max} of insulin glargine metabolite M1), the equivalence criterion (90% CI of the geometric mean ratio (GMR) for test/reference within the limits 80.00% and 125.00%) was met in all the comparisons (Table 6). Also for secondary PK parameters, the 90% CI of the GMR for test/reference lay within these limits (Table 7).

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

Figure 5. Mean plasma M1 concentration versus time profiles by treatment in Study MYL-1501D-1003. The LLOQ of 0.1 ng/mL was shown as a solid line.



Source: Figure 3 of CSR MYL-1501D-1003

Table 6. Summary statistics and comparisons of primary PK parameters in Study MYL-1501D-1003.

Parameter	Statistic	Treatment ¹					
		A (N=87)	B (N=86)	C (N=86)	B vs. A	A vs. C	B vs. C
AUC _{0-24h} (hr*ng/ml)	Geometric LS Mean (SE)	7.20 (0.220)	7.42 (0.222)	7.48 (0.225)	---	---	---
	Intra-subject variability	22.8%	21.8%	21.31%	---	---	---
	Geometric LS Mean Ratio	---	---	---	103.44%	96.47%	99.33%
	Geometric 90% CI Ratio ²	---	---	---	98.91%, 107.28%	92.56%, 99.97%	95.11%, 103.22%
C _{max} (ng/mL)	Geometric LS Mean (SE)	0.43 (0.014)	0.44 (0.014)	0.44 (0.014)	---	---	---
	Intra-subject variability	25.56%	25.19%	22.55%	---	---	---
	Geometric LS Mean Ratio	---	---	---	103.19%	97.41%	99.99%
	Geometric 90% CI Ratio ²	---	---	---	98.07%, 107.52%	93.01%, 101.37%	95.30%, 104.33%

¹ A = MYL-1501D (Process V); B = MYL-1501D (Process VI); C = US Lantus (insulin glargine injection).

² If the intra subject variability in reference treatment <30% and 90% CI of LS mean ratio falls within 80%-125%, PK bioequivalence is demonstrated.

Note: Subject (b) (6) Period 2, (b) (6) Period 1, and (b) (6) Period 3 were excluded from the analysis due to either pre-dose concentration >5% C_{max} or having anomalous spikes in M1 concentrations within 2 hours after dosing.

Source: Table 14 of CSR MYL-1501D-1003

Table 7. Summary statistics and comparisons of secondary PK parameters in Study MYL-1501D-1003

Parameter	Statistic	Treatment ¹					
		A (N=87)	B (N=86)	C (N=86)	B vs. A	A vs. C	B vs. C
AUC _{0-12h} (hr*ng/ml)	Geometric LS Mean (SE)	3.28 (0.112)	3.44 (0.117)	3.60 (0.121)	---	---	---
	Intra-subject variability	26.13%	26.46%	24.63%	---	---	---
	Geometric LS Mean Ratio	---	---	---	105.56%	91.01%	95.47%
	Geometric 90% CI Ratio ²	---	---	---	100.01%, 109.82%	87.34%, 95.40%	91.39%, 100.13%
AUC _{12-24h} (hr*ng/ml)	Geometric LS Mean (SE)	3.87 (0.115)	3.92 (0.114)	3.83 (0.113)	---	---	---
	Intra-subject variability	22.3%	19.55%	23.12%	---	---	---
	Geometric LS Mean Ratio	---	---	---	101.65%	101.89%	102.77%
	Geometric 90% CI Ratio ²	---	---	---	97.50%, 105.50%	96.99%, 105.22%	98.07%, 107.04%
AUC _{0-inf} (hr*ng/ml)	Geometric LS Mean (SE)	12.08 (0.388)	12.51 (0.407)	12.39 (0.400)	---	---	---
	Intra-subject variability	22.24%	21.7%	30.07%	---	---	---
	Geometric LS Mean Ratio	---	---	---	103.22%	NC	NC
	Geometric 90% CI Ratio ²	---	---	---	97.89%, 109.61%	91.78%, 103.48%	95.02%, 107.25%

NC= Not calculable due to incomplete information.

¹ A = MYL-1501D (Process V); B = MYL-1501D (Process VI); C = US Lantus (insulin glargine injection).

² If the intra subject variability in reference treatment <30% and 90% CI of LS mean ratio falls within 80%-125%, PK bioequivalence is demonstrated.

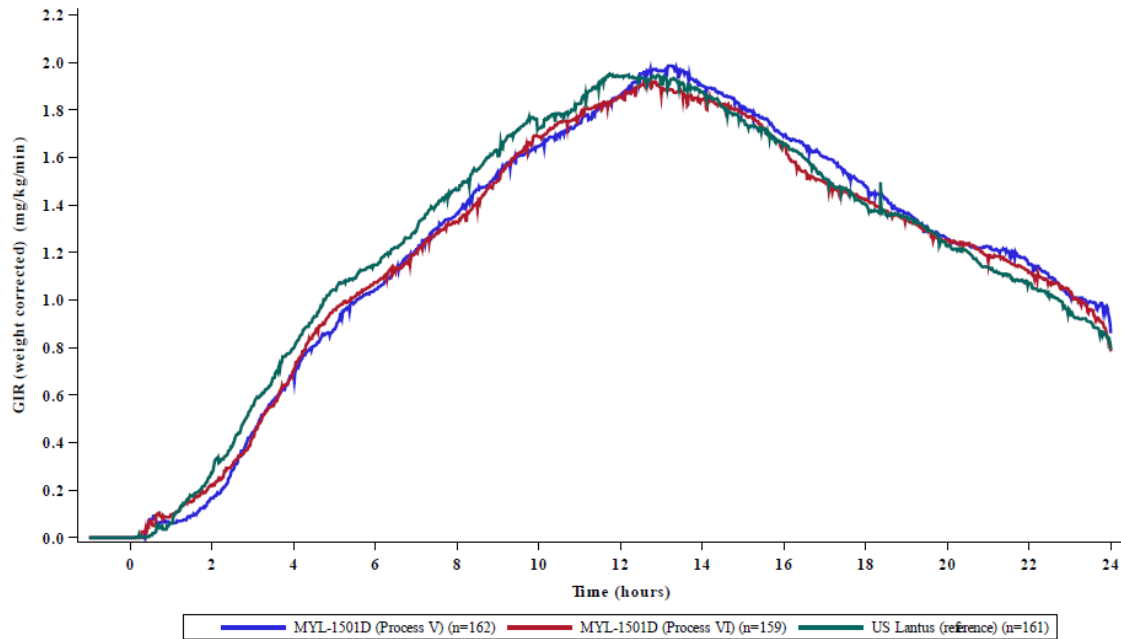
Note: Subject (b) (6) Period 2, (b) (6) Period 1, and (b) (6) Period 3 were excluded from the analysis due to either pre-dose concentration >5% C_{max} or having anomalous spikes in M1 concentrations within 2 hours after dosing.

Source: Table 15 of CSR MYL-1501D-1003

For the PD parameters, Inferential analysis was conducted by the sponsor (Table 8 and Table 9), while the 90% CI for the primary PD parameters were calculated by the reviewer (Table 10). The equivalence criterion (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in both comparisons for the primary PD parameters (AUC_{GIR0-24h} and GIR_{max}), and the secondary PD parameters are similar among treatments.

The results of the sensitivity analyses performed using a clamp CV and deviation from target (DFT) constraint, and C-peptide constraints supported PD similarity between MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection). In addition, blood glucose (Figure 7) and C-peptide were also similar among treatment groups (Figure 8).

Figure 6. Mean glucose infusion rates by treatment in Study MYL-1501D-1003.



Source: Figure 6 of CSR MYL-1501D-1003

Table 8. Summary statistics and comparisons of primary PD parameters in Study MYL-1501D-1003.

Parameter	Statistic	Treatment ¹					
		A (N=86)	B (N=85)	C (N=85)	B vs. A	A vs. C	B vs. C
AUC _{GIR, 0-24h} (mg/kg)	Geometric LS Mean (SE)	1359.15 (108.344)	1396.32 (109.817)	1471.04 (103.524)	---	---	---
	Intra-subject variability	49.67%	40.42%	42.95%	---	---	---
	95% Upper CI ²	---	---	---	-1.462	-1.025	-1.1129
	Point Estimate of Geometric LS Mean Ratio	---	---	---	106.05%	92.25%	98.05%
GIR _{max} (mg/kg/min)	Geometric LS Mean (SE)	1.85 (0.122)	1.84 (0.120)	1.91 (0.115)	---	---	---
	Intra-subject variability	38.01%	31.76%	36.34%	---	---	---
	95% Upper CI ²	---	---	---	-0.0864	-0.0791	-0.0819
	Point Estimate of Geometric LS Mean Ratio	---	---	---	103.89%	96.21%	99.56%

¹ A = MYL-1501D (Process V); B = MYL-1501D (Process VI); C = US Lantus (insulin glargine injection)..

² If the intra subject variability in reference treatment $\geq 30\%$, the 95% upper confidence bound $(\mu - \mu_R)^2 - \theta \sigma^2_{WR} \leq 0$, where $\theta = (\ln \Delta)^2 / \sigma^2_{WR} = [\ln(1.25)/0.25]^2 = 0.797$, and point estimate of geometric LS Mean Ratio between 80% and 125%, then PK or PD bioequivalence will be demonstrated.

Note: Subject (b) (6) Period 1, (b) (6) Period 4, and (b) (6) Period 5 GIR data are excluded from the analysis due to clamp criteria were not met.

Source: Table 18 of CSR MYL-1501D-1003

Table 9. Summary statistics and comparisons of secondary PD parameters in Study MYL-1501D-1003

Parameter	Statistic	Treatment ¹					
		A (N=86)	B (N=85)	C (N=85)	B vs. A	A vs. C	B vs. C
AUC _{GIR,0-12h} (mg/kg)	Geometric LS Mean (SE)	464.07 (51.975)	504.97 (53.992)	552.59 (52.458)	---	---	---
	Intra-subject variability	80.19%	57.15%	67.73%	---	---	---
	95% Upper CI ²	---	---	---	-.3562	-.2223	-.2701
	Point Estimate of Geometric LS Mean Ratio	---	---	---	116.51%	82.72%	91.88%
AUC _{GIR,12-24h} (mg/kg)	Geometric LS Mean (SE)	848.39 (61.922)	856.45 (61.708)	873.05 (53.748)	---	---	---
	Intra-subject variability	47.19%	45.97%	42.36%	---	---	---
	95% Upper CI ²	---	---	---	-.1369	-.1095	-.1110
	Point Estimate of Geometric LS Mean Ratio	---	---	---	101.96%	97.45%	100.68%

¹ A = MYL-1501D (Process V); B = MYL-1501D (Process VI); C = US Lantus (insulin glargine injection).

² If the intra subject variability in reference treatment $\geq 30\%$, the 95% upper confidence bound $(\mu_r - \mu_t)^2 - \theta \sigma_{WR}^2 \leq 0$, where $\theta = (\ln \Delta)^2 / \sigma_{wo}^2 = [\ln(1.25)/0.25]^2 = 0.797$, and point estimate of geometric LS Mean Ratio between 80% and 125%, then PK or PD bioequivalence will be demonstrated.

Note: Subject (b) (6) Period 1, (b) (6) Period 4, and (b) (6) Period 5 GIR data are excluded from the analysis due to clamp criteria were not met.

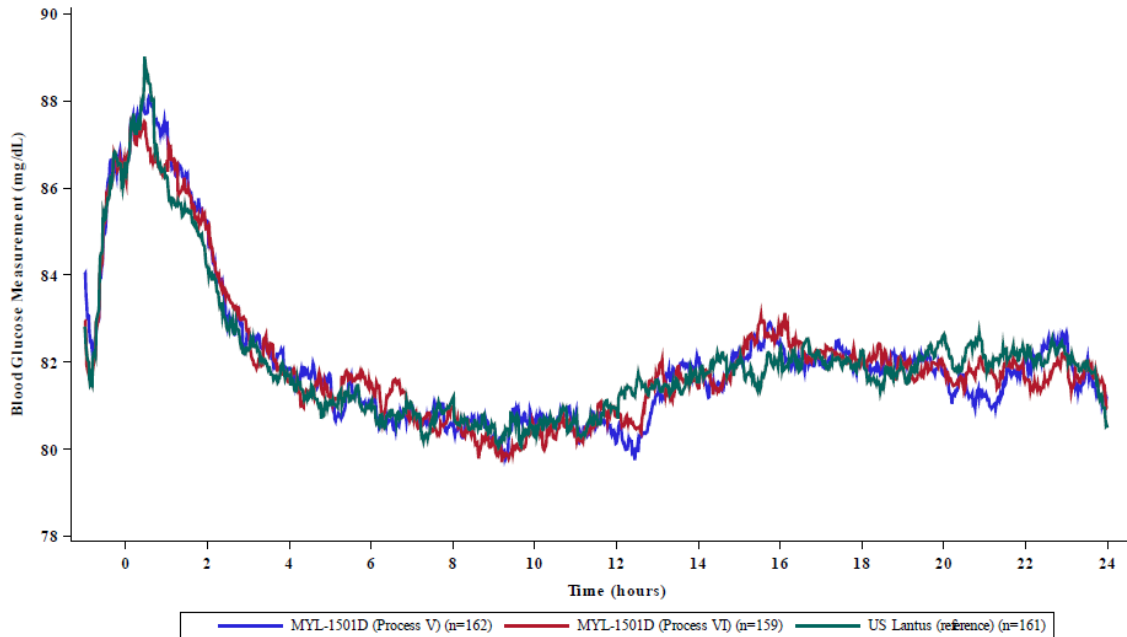
Source: Table 19 of CSR MYL-1501D-1003

Table 10. Treatment comparisons of primary PD parameters in Study MYL-1501D-1003

Parameter	Comparison	N Obs	Geometric LS-mean ratio %	90% CI
AUC _{GIR0-24h}	MYL-1501D (Process VI) vs.US Lantus	85/85	95.84	(87.83; 104.58)
GIR _{max}		85/85	97.55	(90.39; 105.28)
AUC _{GIR0-24h}	MYL-1501D (Process V) vs.US Lantus	86/85	92.25	(84.78; 100.37)
GIR _{max}		86/85	96.38	(90.11; 103.08)
AUC _{GIR0-24h}	MYL-1501D (Process V) vs. MYL-1501D (Process VI)	86/85	103.90	(95.19; 113.39)
GIR _{max}		86/85	101.22	(94.21; 108.74)

Source: Reviewer's analysis

Figure 7. Mean Blood Glucose Concentrations During Clamp by Treatment in Study MYL-1501D-1003

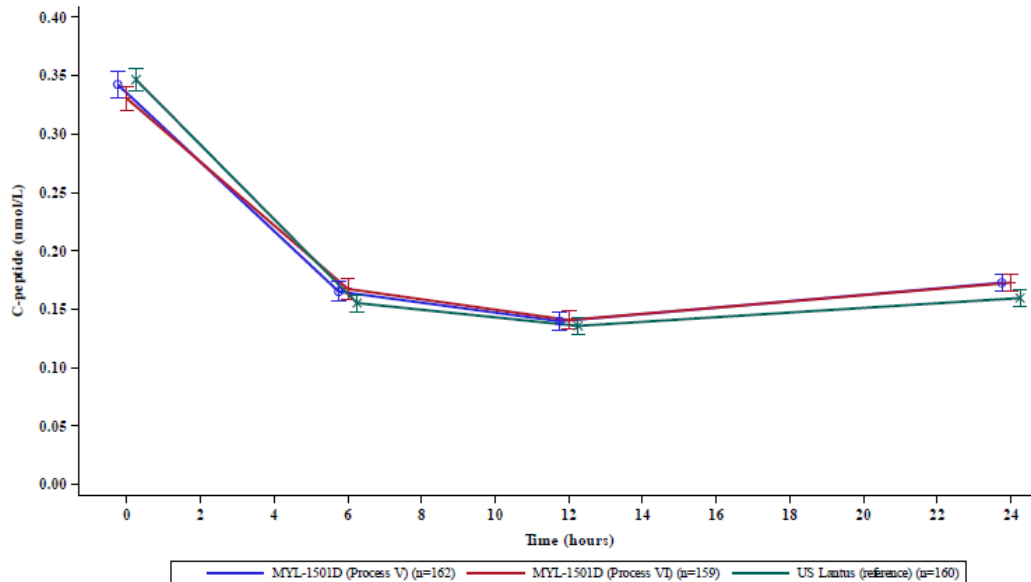


Subjects were planned to take each treatment twice. Measurements from all subjects are summarized by treatment. The n represents the number of records at 0 hours.

Note: Subject (b) (6) Period 1, (b) (6) Period 4, and (b) (6) Period 5 GIR data are excluded from the analysis due to clamp criteria were not met.

Source: Figure 7 of CSR MYL-1501D-1003

Figure 8. Mean Plasma C-peptide Concentrations During Clamp by Treatment



Error bars represent standard errors.

Subjects are planned to take each treatment twice. Measurements from all subjects are summarized by treatment. The n represents the number of pre-dose records.

Source: Figure 10 of CSR MYL-1501D-1003

2.3 Bioanalytical

2.3.1 Are the bioanalytical methods properly validated to measure MYL-1501D and Lantus?

Different bioanalytical methods were used for the quantitation of plasma parent glargine, M1, and M2 metabolites in Study MYL-1501D-1004 (method GLA3HPP Version 001, (b) (4) report 8372478) and Study MY-1501D-1003 (method GIA3HPP, (b) (4) report 8389482).

A comparison was provided in Table 11. Briefly, the method for Study MYL-1501D-1004, GLA3HPP Version 001, utilized a solid phase extraction technique for sample preparation followed by liquid chromatography with tandem mass spectrometric detection (LC MS/MS), and was validated over a range from 0.2 ng/mL to 3.0 ng/mL for all analytes. While the method for Study MYL-1501D-1003, GIA3HPP, employed an immunoaffinity extraction technique for sample preparation followed by LC MS/MS, and was validated over a range of 0.1 to 1.5 ng/mL for all analytes. No cross-validation were performed to compare the two methodologies.

Each of the analytical method were fully validated in accordance with the Bioanalytical Method Validation guidance from the agency¹. See Table 12 and Table 13 for the summary of assay validation for in Study MYL-1501D-1004 and Study MYL-1501D-1003, respectively. Overall, the bioanalytical assay for measuring MYL-1501D and Lantus are acceptable with reasonable accuracy and precision.

It's worth mentioning that those methods are also different from the method for Study MYL-1501D-1001 in the original submission (method HB-13-017, (b) (4) Study Report 82864841) (Table 11).

However, the reviewer noted that the stability of the analytes in plasma (long-term, freeze-thaw, benchtop and whole blood) established during method HB-13-017 validation was applied to GLA3HPP Version 001. While the stability profile is currently ongoing for method GIA3HPP: results from the most recently completed timepoint of 186 days (6 months) are well within acceptance limits, and a final timepoint at 12 months storage duration is planned for August 2019, which will provide the coverage necessary for the maximum storage intervals for study samples from Study MYL-1501D-1003 (317 days). The applicant's justification is reasonable. Since the stability in matrix has been established for a long-term stability of 1416 days at -80°C with the method HB-13-017 in the original submission and the results from Study MYL-1501D-1003 are reassuring of the findings from Study MYL-1501D-1001, there are no further concerns with regards to stability data and reliability of the associated PK data for the resubmission.

The high PK profile exclusion in Study MYL-1501D-1004 was not observed in Study MYL-1501D-1003. The difference in assay sensitivity is the most plausible reason as the LLOQ was improved from 0.2 ng/mL (Method GLA3HPP Version 001 for Study MYL-1501D-1004) to 0.1 ng/mL (Method GIA3HPP for MYL-1501D-1003). To avoid risks of study failures, the Applicant should use a sensitive bioanalytical method to adequately characterize the PK profile of MYL-1501D and Lantus in PKPD studies, as they did in the case for Study MYL-1501D-1003.

¹ <https://www.fda.gov/media/70858/download>

Table 11. Study overview and bioanalytical summary of study MYL-1501D-1001, MYL-1501D-1004, and study MYL-1501D-1003

Study ID	MYL-1501D-1001	MYL-1501D-1004	MYL-1501D-1003
Study Overview			
Test Product	- MYL-1501D (Process V in cartridges) - MYL-1501D (Process VI in cartridges) - Lantus US	- MYL-1501D (process VI in vials) - MYL-1501D (process VI in cartridges)	- MYL-1501D (Process V in cartridges) - MYL-1501D (Process VI in cartridges) - Lantus US
Study Design	Crossover design	Fully replicated crossover design	Fully replicated crossover design
Dosage Regimen	Single dose of 0.5 IU/kg		
Participants	T1DM	Healthy Subjects	Healthy Subjects
Clinical Site	- Profil Neuss (Germany) - Profil Mainz (Germany)		ProSciento, Inc (California)
Bioanalytical			
Site	(b) (4)		
Detection method	LC-MS/MS		
Method #	HB-13-017	GLA3HPP Version 001	GIA3HPP
Bioanalytical method validation report name	Section 5.3.1.4 (b) (4) Study Report 8286484 (Sequence 0000)	Section 5.3.1.4 (b) (4) Study Report 8372478 (Sequence 0045)	Section 5.3.1.4 (b) (4) Study Report 8389482 (Sequence 0045)
Biological Matrix	K ₂ EDTA Plasma, Normal healthy and T1DM	K ₂ EDTA Plasma, Normal healthy only	K ₂ EDTA Plasma, Normal healthy and T1DM
Extraction Method	Solid Phase extraction	Solid Phase extraction	Immunoaffinity Extraction
Validated range	0.2 to 5 ng/mL, all analytes	0.2 to 3 ng/mL, all analytes	0.1 to 1.5 ng/mL, all analytes
Methodological changes	Original	Chromatographic conditions, MS source condition optimized for API6500+ platform Truncated upper analytical range and adjusted QC levels	Extraction Method Chromatographic conditions Lowered LLOQ and adjusted analytical range
Cross-validation	No cross-validation conducted		

Table 12. Summary of assay validation for determination of insulin glargine and two metabolites (glargine M1 and M2) using analytical method GLA3HPP for Study MYL-1501D-1004.

Analytes	Insulin Glargine Glargine M1 Glargine M2
Species	Human
Analytical matrix	K ₂ EDTA Plasma
Internal standards (ISTD)	Glargine stable isotope labelled (SIL) Glargine M1 stable isotope labelled (SIL) Glargine M2 stable isotope labelled (SIL)
Validated method	GLA3HPP
Validated range	0.2, 0.3, 0.5, 0.9, 1.5, 2.7 and 3.0 ng/mL
Quality Control (QC) levels	0.2 ng/mL, 0.3 ng/mL, 0.6 ng/mL, 1.2 ng/mL, 2.4 ng/mL, 10 ng/mL
Analytical technique/detection method	Solid-phase extraction / LC-MS/MS
Sample volume	300 µL
Calibration model	Linear regression
Weighting factor	1/x
Accuracy and precision	Requirements fulfilled
ISTD response mean %RSD	Glargine: 7.3% Glargine M1: 8.1% Glargine M2: 9.0%
Maximum run size	120 injections
Dilution	10 ng/mL at 10-fold dilution factor confirmed
Run blank and interference of analyte on internal standard	Passes acceptance criteria
Effect of analytes not measured with the assay	Actrapid – 2.5 ng/mL Passes acceptance criteria
Carryover	Passes acceptance criteria
Matrix selectivity and matrix effect	Passes acceptance criteria for normal human Plasma (K ₂ EDTA) Not within acceptance criteria for T1DM plasma
Matrix factor (MF)	Passes acceptance criteria
Extraction recovery	Passes acceptance criteria
Haemolysis	Passes acceptance criteria
Hyperlipidaemia	Passes acceptance criteria
Solution Stability – Stored Primary standard solutions	Glargine: 37 days at nominal -80°C Glargine M1: 37 days at nominal -80°C Glargine M2: 37 days at nominal -80°C
Solution stability – Bench top Intermediate standard solutions	Glargine stable isotope labelled (SIL): 23 hours on wet ice Glargine M1 stable isotope labelled (SIL): 23 hours on wet ice Glargine M2 stable isotope labelled (SIL): 23 hours on wet ice
Processed sample stability	Glargine: 216 hours at nominal 5°C Glargine M1: 216 hours at nominal 5°C Glargine M2: 216 hours at nominal 5°C

Abbreviations: K₂EDTA: dipotassium ethylenediaminetetraacetic acid, SIL: stable isotopic label, T1DM: type 1 diabetes mellitus.

Source: section 2.7.1.2.2 of the summary of biopharmaceutic studies and associated analytical methods

Table 13. Summary of assay validation for determination of insulin glargine and two metabolites (glargine M1 and M2) using analytical method GIA3HPP for Study MYL-1501D-1003.

Analytes	Insulin Glargine Glargine M1 Glargine M2
Species	Human
Analytical matrix	K ₂ EDTA Plasma
Internal standards (ISTD)	Glargine stable isotope labelled (SIL) Glargine M1 stable isotope labelled (SIL) Glargine M2 stable isotope labelled (SIL)
Validated method	GIA3HPP
Validated range	0.1, 0.18, 0.35, 0.6, 0.9, 1.35 and 1.5 ng/mL
Quality Control (QC) levels	0.1 ng/mL, 0.25 ng/mL, 0.5 ng/mL, 1.2 ng/mL, 5 ng/mL
Analytical technique/detection method	Immunoaffinity extraction / LC-MS/MS
Sample volume	225 µL
Calibration model	Linear regression
Weighting factor	1/x
Accuracy and precision	Requirements fulfilled
ISTD response mean %RSD	Glargine: 4.6% Glargine M1: 6.8% Glargine M2: 6.0%
Maximum run size	192 injections
Run blank and interference of analyte on internal standard	Passes acceptance criteria
Effect of analytes not measured with the assay	Actrapid – 2.5 ng/mL: Passes acceptance criteria Insulin Glulisine – 0.5 ng/mL: Passes acceptance criteria Insulin Lispro – 5 ng/mL: Passes acceptance criteria
Carryover	Passes acceptance criteria
Matrix selectivity and matrix effect	Passes acceptance criteria for normal healthy human Plasma (K ₂ EDTA) Passes acceptance criteria for T1DM Plasma (K ₂ EDTA)
Matrix factor (MF)	Passes acceptance criteria
Extraction recovery	Passes acceptance criteria
Haemolysis	Passes acceptance criteria
Hyperlipidemia	Passes acceptance criteria
Anti-Drug Antibody Effect on Assay	Acceptable
Individually Spiked HQC's to Assess Competitive Binding	Acceptable
Solution stability – Bench top	Intermediate standard solutions Glargine stable isotope labelled (SIL): 24 hours on wet ice Glargine M1 stable isotope labelled (SIL): 24 hours on wet ice Glargine M2 stable isotope labelled (SIL): 24 hours on wet ice
Matrix bench-top stability	6 hours on wet ice
Matrix freeze-thaw stability	3 cycles at nominal -20°C 3 cycles at nominal -80°C
Long-term frozen matrix stability (in healthy donor plasma)	99 days at nominal -20°C 129 days at nominal -80°C
Processed sample stability	Glargine: 94 hours at nominal 5°C Glargine M1: 94 hours at nominal 5°C Glargine M2: 94 hours at nominal 5°C
Stability in blood	2 hours at room temperature 2 hours on wet ice

Source: section 2.7.1.2.3 of the summary of biopharmaceutic studies and associated analytical methods

2.3.2 Was an Office of Study Integrity and Surveillance (OSIS) inspection requested for the clinical study?

The Division of Metabolism and Endocrinology Products requested an OSIS inspection for the clinical and bioanalytical sites of MYL-1501D-1001 through Michael G White dated April 10, 2019 (Reference ID: 4417609 in DARRTS).

The Division of New Drug Bioequivalence Evaluation within OSIS declined to conduct an on-site inspection for the clinical and bioanalytical sites of Study MYL-1501D-1004: the clinical and bioanalytical sites were inspected for the original submission of NDA210605 in January 2018 and (b) (4), respectively, which falls within the surveillance interval. The bioanalytical site of Study MYL-1501D-1003 is the same as that of Study MYL-1501D-1004, thus was declined as well. See memorandum dated May 3, 2019 (Reference ID: 4428832 in DARRTS) for details.

For the clinical site of Study MYL-1501D-1003, an inspection was conducted and the final inspection classification for the inspected site is No Action Indicated (NAI). See memorandum dated May 8, 2019 (Reference ID: 4430102 in DARRTS) for details.

A summary of the clinical and bioanalytical sites of study MYL-1501D-1001, MYL-1501D-1004 and MYL-1501D-1003 were provided in Table 11.

Overall, OSIS recommended that data from Study MYL-1501D-1004 and MYL-1501D-1003 be accepted for Agency review.

3 Preliminary Labeling Recommendations

Note: Labeling Comments are provided for specific sections in the proposed label. The underlined **RED** text indicates comments to apply.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

12.2 Pharmacodynamics

The pharmacodynamic profile for SEMGLEE was determined after subcutaneous administration of a single 0.5 U/kg dose in a euglycemic clamp study conducted in 116 type 1 diabetes patients. The median time to maximum effect of SEMGLEE (measured by the peak rate of glucose infusion) was

approximately 11.3 hours. The pharmacodynamic profile of SEMGLEE following subcutaneous injection demonstrated sustained glucose lowering activity over 24 hours with no pronounced peak. The arithmetic mean area under the glucose infusion rate curves (AUC GIR 0-^{(b) (4)}24h) and maximum glucose infusion rate ^{(b) (4)}1423 mg/kg and ^{(b) (4)}1.855 mg/kg/min, respectively.

The time course of action of insulins, including SEMGLEE, may vary between individuals and within the same individual.

Comment to applicant: should use the mean value from process VI instead of process V

12.3 Pharmacokinetics

Absorption- (b) (4)

After subcutaneous injection of a single 0.5 U/kg dose of SEMGLEE in a euglycemic clamp study conducted in 116 type 1 diabetes patients, the M1 active metabolite plasma concentration profile indicated a prolonged absorption and a relatively constant concentration/time profile over 24 hours.

The median time to maximum M1 plasma concentration was 12 hours after injection. The mean plasma observed area under the concentration-time curve for M1 from time zero to 24 hours and peak plasma concentration were 10.5 (b) (4) ng*hr/mL and (b) (4) ng/mL, respectively.

(b) (4) Elimination-

Metabolism

A metabolism study in humans indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with in vitro activity similar to that of human insulin, M1 (21^A-Gly-insulin) and M2 (21^A-Gly-des30^B-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

Special Populations:

Age, Race, and Gender

±Effect of age, race, and gender on the pharmacokinetics of SEMGLEE has not been evaluated.

Obesity

±Effect of Body Mass Index (BMI) on the pharmacokinetics of SEMGLEE has not been evaluated.

Comment to applicant: headings updated according to PK Guidance.

4 Appendix

4.1 Synopsis of Study MYL-1501D-1004

Name of Sponsor/Company: Mylan GmbH Thurgauerstrasse 40 8050 Zurich, Switzerland	
Name of Finished Test Products: MYL-1501D Process VI formulations (developmental products)	
Name of Active Ingredients: Insulin glargine	
Title of Trial: A glucose clamp trial investigating the bioequivalence of MYL-1501D formulation in vials versus MYL-1501D formulation in cartridges in healthy volunteers	
Coordinating Investigator: Oliver Klein, Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany	
Trial Centers: Profil Institut für Stoffwechselforschung GmbH, Hellersbergstraße 9, 41460 Neuss, Germany (Profil Neuss) Profil Mainz GmbH & Co. KG, Malakoff-Passage, Rheinstraße 4C, 55116 Mainz, Germany (Profil Mainz)	
Publication (Reference): Unpublished	
Trial Period: 11 Dec 2017 (FSFV) – 04 Apr 2018 (LSLV)	Phase of Development: I
Background for the Trial: The aim of this trial was to demonstrate bioequivalence between the MYL-1501D formulation in vial with polysorbate and the MYL-1501D formulation in cartridge without polysorbate based on similar pharmacokinetics (PK) and pharmacodynamics (PD). Demonstration of bioequivalence between the vial and cartridge formulation would allow to bridge results from clinical studies conducted with either cartridges or vials.	
Objectives: <u>Primary objective:</u> • To demonstrate PK and PD equivalence of MYL-1501D formulation in vial compared to MYL-1501D formulation in cartridge. <u>Secondary objectives:</u> • To compare the PK and PD secondary parameters of MYL-1501D formulation in vial with MYL-1501D formulation in cartridge • To assess the safety and tolerability of MYL-1501D formulation in vial and MYL-1501D formulation in cartridge	
Methodology: The trial was a Phase 1, two-center, randomized, double-blind, 4-way crossover, fully replicated, 2-treatment trial comparing single doses of MYL-1501D Process VI in vial with polysorbate with MYL-1501D Process VI in cartridges without polysorbate. A crossover, fully replicated design was chosen in order to use scaled bioequivalence method. The replicate design provides information on the actual intra-subject variability of the investigational medicinal products (IMPs) in this trial, which can be used to perform scaled bioequivalence analyses. Each subject participated in 7 visits: an informed consent visit (at least one day before Visit 1), a	

screening visit (Visit 1, 1 to 28 days before Visit 2) to check eligibility for participation, 4 dosing visits (Visits 2, 3, 4 and 5, separated by a washout period of 5 to 21 days), and a follow-up visit with final examination (Visit 6, 1 to 10 days after Visit 5). At Visits 2, 3, 4 and 5, the 2 insulin products were administered in 2 randomly allocated sequences in the setting of a 24-hour computer-controlled euglycemic glucose clamp (glucose clamp target: 81 mg/dL; ClampArt). During the clamp procedure, blood was collected pre-dose and at pre-specified intervals until 24 hours post-dose for measurement of blood glucose (for verifying ClampArt measurements) and insulin glargine metabolite 1 (M1). Safety assessments included vital signs recording, electrocardiograms (ECGs), laboratory safety parameters, physical examination, and recording of adverse events (AEs).

Number of Subjects:

Forty-eight (48) subjects were planned to be randomized to ensure that 42 subjects completed the trial. Actually, 48 subjects were randomized and 45 completed the trial.

Diagnosis and Main Criteria for Inclusion:

Healthy male or female subjects from age 18 to 65 years (both inclusive), a body mass index (BMI) between 18.5 and 29.9 kg/m² (both inclusive) and fasting plasma glucose (FPG) < 100 mg/L were allowed to participate in the trial after having given written informed consent. Subjects were excluded from participation if they met any of the exclusion criteria defined in the trial protocol.

Test Products, Dose and Mode of Administration, Batch Number:

- MYL-1501D Process VI insulin glargine, 100 U/mL in 10 mL vials with polysorbate.
Manufacturer: Biocon sdn, Malaysia, manufacturing batch no.: BS16002122, packaging batch no.: BS16002425; expiry date: 05/2018.
 - MYL-1501D Process VI insulin glargine, 100 U/mL in 3 mL cartridges without polysorbate.
Manufacturer: Biocon sdn, Malaysia, manufacturing batch no.: BS15009374, packaging batch no.: BS16000035; expiry date: 08/2018.
- Single dose of 0.5 U/kg body weight by using a disposable syringe with a needle length of 10 mm (BD Plastipak™ 1 ml Test 27 G 3/8), administered s.c. at Visits 2, 3, 4 or 5.

Duration of Treatment:

The planned trial duration per subject was approximately 5 weeks (range 3-15 weeks). The treatment consisted of 4 single dose administrations, 2 of each test product (replicates R1 and R2), separated by 5 to 21 days between dosing visits.

Control Products, Dose and Mode of Administration, Batch Number:

There were none in this trial. Both IMPs were test products.

Endpoints:

Primary Pharmacokinetic Endpoints:

- AUC_{0-24h}, area under the insulin glargine metabolite 1 (M1) concentration curve from 0 to 24 hours
- C_{max}, maximum observed insulin glargine M1 concentration

Primary Pharmacodynamic Endpoints:

- AUC_{GIR,0-24h}, area under the glucose infusion rate curve from 0 to 24 hours
- GIR_{max}, maximum observed glucose infusion rate

Secondary Pharmacokinetic Endpoints:

- AUC_{0-12h}, AUC_{12-24h}, AUC_{0-inf}, area under the insulin glargine M1 concentration curve in the indicated time intervals
- t_{max}, time to maximum observed insulin glargine M1 concentration
- t_{1/2}, terminal elimination half-life calculated as $t_{1/2} = \ln 2 / \lambda_z$
- λ_z , terminal elimination rate constant

Secondary Pharmacodynamic Endpoints:

- $AUC_{GIR,0-12h}$, $AUC_{GIR,12-24h}$, areas under the glucose infusion rate curve in the indicated time-intervals
- $t_{max,GIR}$, time to maximum glucose infusion rate

Safety Endpoints:

- AEs including hypoglycemic episodes and injection site reactions, clinical laboratory safety parameters, physical examination, vital signs, and ECGs

Statistical Methods:

Statistical PK analyses were performed by the Sponsor and PD, safety and other remaining analyses by statisticians of Profil Neuss. Statistical analyses were performed using SAS[®] (SAS Institute Inc., Cary, North Carolina, USA), Version 9.3 (PK analyses) and 9.4 (remaining analyses).

PK endpoints were derived from individual plasma insulin M1 profiles, and PD endpoints from individual glucose infusion rate (GIR) profiles. Primary PK and PD endpoints were analyzed using logarithm-transformed data and the scaled average bioequivalence (SABE) approach (Haidar et al.*). SABE method was applied if the estimate for the within reference intra-subject variance (s_{WR}) was ≥ 0.294 , with the reference being defined as MYL-1501D formulation in cartridge. Bioequivalence was demonstrated if the upper 95% confidence bound of the SABE metric was below zero and the ratio of the geometric LS-means (vial/cartridge) fell within 80.00 and 125.00%. If s_{WR} was < 0.294 then a linear mixed model for repeated measurements was employed, and bioequivalence was demonstrated if the 90% confidence interval (CI) of the geometric LS-mean ratio of treatments (vial/cartridge) fell within the limits of 80.00 to 125.00%. The trial site by treatment interaction was not significant and therefore dropped from the models. Secondary PK and PD AUC endpoints were analyzed with the same statistical approach but did not need to fulfil respective limits for bioequivalence. All PK/PD endpoints, including t_{max} , $t_{1/2}$, λ_z , and $t_{max,GIR}$, were presented by summary statistics. Descriptive summaries and analyses were based on the per-protocol population (PPP) for PK and for PD.

For PD analyses and summary statistics dosing periods with low responses or insufficient clamp quality according to criteria pre-defined in the statistical analysis plan (SAP) could be excluded, but such criteria were not met. A sensitivity analysis for primary PD endpoints excluded profiles with increases in C-peptide concentrations according to criteria pre-defined in the SAP.

For PK analyses and summary statistics dosing periods with less than 50% of the post-dosing concentrations above the lower limit of quantification were excluded, according to criteria pre-defined in the protocol and SAP. Likewise subjects who discontinued the trial or had no evaluable measurements for at least 1 dosing period per treatment (i.e. at least one replicate measurement) were excluded. For one subject, the last dosing period was omitted from the calculation of the primary and certain secondary PK endpoints due to missing values.

Safety endpoints were analyzed based on the safety analysis set. Safety was evaluated by AEs including hypoglycemic episodes and injection site reactions, clinical laboratory tests, vital signs, ECGs and physical examinations. Safety results and the change from baseline were presented using descriptive statistics by visit/treatment.

* Haidar SH, Davit B, Chen ML, Conner D, Lee L, Li QH, et al. Bioequivalence approaches for highly variable drugs and drug products. *Pharm Res.* 2008;25(1):237-41.

RESULTS – SUMMARY

Subject Disposition, Demographic and Baseline Characteristics:

In total 48 subjects (20 at trial site Neuss and 28 at trial site Mainz) were randomized to one of the 2 treatment sequences. Three (3) subjects (6.3%) prematurely discontinued trial participation after randomization and at least 1 dose administration, all on own initiative. Thus, 48 subjects with age from 21 to 60 years (mean = 41.3 years), BMI from 19.0 to 29.9 kg/m² (mean = 25.22 kg/m²) and FPG values between 58 and 99 mg/dL (mean $\pm$ SD of 89.5 $\pm$ 7.10 mg/dL) were exposed to at least one dose of IMP, and were included in the safety analysis set. The 45 completers of the trial were included in the

PPP for PD. In the PPP for PK, which comprised 40 subjects, 5 additional subjects were excluded due to the rules outlined in the protocol and SAP (see also preceding section on statistical methods). The demographic and baseline characteristics were comparable in both trial centers.

Pharmacokinetic Results:

The following tables display the summary statistics of the PK endpoints by treatment and the results of the statistical comparisons (PPP for PK).

Statistics	MYL-1501D (vial)			MYL-1501D (cartridge)		
	AUC ₀₋₂₄ (h ⁺ ng/mL)	C _{max} (ng/mL)		AUC ₀₋₂₄ (h ⁺ ng/mL)	C _{max} (ng/mL)	
N Obs	70	70		72	72	
Mean	6.237	0.391		6.384	0.404	
SD	1.722	0.089		1.979	0.109	
	AUC ₀₋₁₂ (h ⁺ ng/mL)	AUC ₁₂₋₂₄ (h ⁺ ng/mL)	AUC _{0-inf} (h ⁺ ng/mL)	AUC ₀₋₁₂ (h ⁺ ng/mL)	AUC ₁₂₋₂₄ (h ⁺ ng/mL)	AUC _{0-inf} (h ⁺ ng/mL)
N Obs	70	70	43	73	72	42
Mean	2.789	3.448	13.078	2.837	3.542	12.127
SD	0.970	0.960	5.652	1.177	1.005	3.162
	t _{max} (h)	t _{1/2} (h)	λ _z (/h)	t _{max} (h)	t _{1/2} (h)	λ _z (/h)
N Obs	70	43	43	72	42	42
Mean	12.24	17.83	0.0518	13.12	14.11	0.0586
SD	3.14	12.80	0.0250	3.75	7.10	0.0234
Min	3.00	4.79	0.0101	6.00	4.96	0.0158
Median	12.00	14.38	0.0482	13.18	11.66	0.0594
Max	20.00	68.80	0.1448	24.00	43.92	0.1398

N Obs: Number of observations; Mean: Arithmetic mean; SD: Standard deviation; Min: Minimum; Max: Maximum; Lambda-dependent parameters with R²<0.8 not presented.

Parameter	Comparison	N Obs	Geometric LS-mean ratio %	90% CI	SABE _{SWR}	SABE ratio%	SABE criteria bound
AUC _{0-24h}	MYL-1501D vial vs. cartridge	70/72	97.82	(90.33; 105.94)	0.2837	NA	NA
C _{max}	MYL-1501D vial vs. cartridge	70/72	97.80	(91.55; 104.48)	0.2373	NA	NA
AUC _{0-12h}	MYL-1501D vial vs. cartridge	70/73	99.57	(90.26; 109.84)	0.3361	101.50	-0.0584
AUC _{12-24h}	MYL-1501D vial vs. cartridge	70/72	97.31	(88.95; 106.46)	0.3514	97.32	-0.0656
AUC _{0-inf}	MYL-1501D vial vs. cartridge	43/42	104.91	(95.47; 115.28)	0.1900	NA	NA

NA: Not applicable;

For the primary PK endpoints, AUC_{0-24h} and C_{max} of insulin glargine metabolite M1, the mixed linear model was employed, and the bioequivalence criterion (90% CI of the ratio MYL-1501D vial/cartridge within the limits 80.00 and 125.00%) was met. Also for the secondary endpoint AUC_{0-inf}, the 90% CI of the ratio MYL-1501D vial/cartridge fell within the limits of 80.00 and 125.00%. For AUC_{0-12h} and AUC_{12-24h} both SABE criteria were met. The 95% upper confidence limit (SABE criteria bound) was lower than zero and the SABE geometric mean ratio (vial/cartridge) fell within 80.00 and 125.00%.

Pharmacodynamic Results:

The following tables display the summary statistics of the PD endpoints by treatment and the results of the statistical comparisons (PPP for PD).

Parameter	Treatment	N Obs	Mean	SD	Min	Median	Max
AUC _{GIR,0-24h} [mg/kg]	MYL-1501D (vial)	90	54.592	26.6264	14.13	51.094	134.62
	MYL-1501D (cartridge)	90	54.757	26.5083	11.04	49.674	129.97
GIR _{max} [mg/kg/min]	MYL-1501D (vial)	90	3.486	1.7309	1.26	3.157	10.22
	MYL-1501D (cartridge)	90	3.520	1.6958	0.75	3.281	9.30
AUC _{GIR,0-12h} [mg/kg]	MYL-1501D (vial)	90	27.485	13.0553	9.91	25.324	77.10
	MYL-1501D (cartridge)	90	27.401	13.7929	5.23	25.125	67.39
AUC _{GIR,12-24h} [mg/kg]	MYL-1501D (vial)	90	27.106	14.5642	4.22	24.438	61.85
	MYL-1501D (cartridge)	90	27.356	13.9241	5.25	25.195	62.58
t _{maxGIR} [h]	MYL-1501D (vial)	90	10.954	4.5412	2.60	10.233	24.00
	MYL-1501D (cartridge)	90	11.528	5.2511	3.82	10.950	24.00

N Obs: Number of observations; Mean: Arithmetic mean; SD: Standard deviation; Min: Minimum; Max: Maximum

Parameter	Comparison	N Obs	Geometric LS-mean ratio	90% CI	SABE _{WR}	SABE ratio%	SABE criteria bound
AUC _{GIR,0-24h}	MYL-1501D vial vs. cartridge	90/90	99.98	(93.96;106.39)	0.253	NA	NA
GIR _{max}	MYL-1501D vial vs. cartridge	90/90	99.54	(93.52;105.95)	0.278	NA	NA
AUC _{GIR,0-12h}	MYL-1501D vial vs. cartridge	90/90	102.63	(95.93;109.79)	0.295	102.95	-0.0485
AUC _{GIR,12-24h}	MYL-1501D vial vs. cartridge	90/90	96.93	(89.82;104.60)	0.280	NA	NA

For the primary PD endpoints, AUC_{GIR,0-24h} and GIR_{max}, the mixed linear model was employed, and the bioequivalence criterion (90% CI of the ratio MYL-1501D vial/cartridge within the limits 80.00 and 125.00%) was met. Also for the secondary endpoint AUC_{GIR,12-24h}, the 90% CI of the ratio MYL-1501D vial/cartridge fell within the limits 80.00 and 125.00%. For AUC_{GIR,0-12h} both SABE criteria were met. The 95% upper confidence limit (SABE criteria bound) was lower than zero and the geometric mean ratio (vial/cartridge) fell within 80.00 and 125.00%.

The sensitivity analysis of primary PD endpoints excluding dosing periods with increases of C-peptide had no impact on the results, and the bioequivalence criterion was met.

Safety:

At least one treatment-emergent AE (TEAE) was experienced by 14 subjects (29.2%) after administration of MYL-1501D from the vial formulation and by 11 subjects (23.4%) after administration of MYL-1501D from the cartridge formulation. The respective numbers of single events were 17 for each of the formulations, yielding a total number of 34 TEAEs.

No serious adverse events or deaths occurred, and none of the AEs resulted in a subject's discontinuation from the trial. The majority of AEs were mild (19 events), 15 AEs were moderate in severity, and none of the events was considered severe. Four (4) TEAEs (2 headaches and 2 injection site reactions) after MYL-1501D (vial) and none after MYL-1501 D (cartridge) were assessed as possibly or probably related to IMP administration. Except for one TEAE (infusion site pain after MYL-1501D (cartridge) with outcome recovering/resolving) all TEAEs had the outcome recovered/resolved.

Most frequent TEAE based on the preferred term level was headache (14.6% subjects after MYL-

1501D (vial) and 10.6% subjects after MYL-1501D (cartridge) and nasopharyngitis (2.1% subjects after MYL-1501D (vial) and 6.4% subjects after MYL-1501D (cartridge)). Only 2 mild local tolerability findings occurred in connection with IMP injection and were assessed as possibly or probably related to trial procedures. No hypoglycemic event occurred in this trial.

Besides a transient increase in creatine phosphokinase reported as an AE, there were no clinically significant findings or changes in safety laboratory test results. There were no clinically significant findings or changes in vital signs, ECGs, and physical examination results.

CONCLUSIONS:

Pharmacokinetics:

- Based on the primary PK endpoints, AUC_{0-24h} and C_{max} of the insulin glargine metabolite M1, both formulations of MYL-1501D Process VI (vial and cartridge) were bioequivalent, since the 90% CIs of the respective geometric LS-mean ratios vial/cartridge lay within the acceptance interval of 80.00 to 125.00%.
- Results of all secondary PK AUC endpoints (AUC_{0-12h} , AUC_{12-24h} and AUC_{0-inf}) fell within 80.00 to 125.00% limits and further supported PK bioequivalence of both MYL-1501D Process VI formulations.

Pharmacodynamics:

- Based on the primary PD endpoints, $AUC_{GIR,0-24h}$ and GIR_{max} , both formulations of MYL-1501D Process VI (vial and cartridge) were bioequivalent, since the 90% CIs of the respective geometric LS-mean ratios vial/cartridge lay within the acceptance interval of 80.00 to 125.00%.
- Results of all secondary PD AUC endpoints ($AUC_{GIR,0-12h}$ and $AUC_{GIR,12-24h}$) fell within 80.00 to 125.00% limits and further supported PK bioequivalence of both MYL-1501D Process VI formulations.

Safety:

- Both MYL-1501D Process VI formulations (vial and cartridge) were well tolerated at single s.c. doses of 0.5 U/kg, when administered to healthy male and female subjects.
- The safety profiles of both MYL-1501D Process VI formulations (vial and cartridge) were similar.

Overall Conclusion:

- Overall, based on the results of this trial, both formulations of MYL-1501D Process VI (vial and cartridge) can be considered as bioequivalent, and the safety profiles of both formulations were similar.

Date of Report: 31 Aug 2018 (Final Version 1.0)

4.2 Synopsis of Study MYL-1501D-1003

Background and Rationale for the Study

US licensed Lantus® (insulin glargine injection) is a long-acting insulin analogue with insulin glargine as the active ingredient. It is indicated for once daily subcutaneous administration in subjects with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). It has been developed by Sanofi (formerly Sanofi-Aventis) and has been marketed in both Europe and the United States (US) since the year 2000.

MYL-1501D is a long-acting insulin glargine analogue developed by Mylan GmbH that has an identical amino acid sequence and similar structure to US Lantus (insulin glargine injection). MYL-1501D is produced using two manufacturing processes.

This study was conducted to demonstrate pharmacokinetic (PK) and pharmacodynamic (PD) equivalence of insulin glargine between MYL-1501D (Process V), MYL-1501D (Process VI), and the reference product US Lantus (insulin glargine injection) in healthy subjects. Demonstration of PK and PD equivalence between these products is an important consideration to achieve marketing authorization for MYL-1501D.

Objectives and Outcome Measures

Primary Objectives and Endpoints

1. To demonstrate PK and PD equivalence of insulin glargine between MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) as assessed by:
 - a. Primary PK endpoints:
 - i. Area under the insulin glargine metabolite 1 (M1) concentration curve from 0 to 24 hours (AUC_{0-24h}).
 - ii. Maximum observed insulin glargine M1 concentration (C_{max}).
 - b. Primary PD endpoints:
 - i. Area under the glucose infusion rate curve from 0 to 24 hours ($AUC_{GIR,0-24h}$).
 - ii. Maximum glucose infusion rate (GIR_{max}).

Secondary Objectives and Endpoints

1. To compare the PK and PD parameters of MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) as assessed by:
 - a. Secondary PK endpoints:
 - i. Area under the insulin glargine M1 concentration curve in the indicated time intervals (AUC_{0-12h} , AUC_{12-24h} , AUC_{0-inf}).
 - ii. Time to maximum observed insulin glargine M1 concentration (t_{max}).
 - iii. Terminal elimination half-life calculated as $t_{1/2} = \ln 2 / \lambda_z$ ($t_{1/2}$).
 - iv. Terminal elimination rate constant (λ_z).
 - b. Secondary PD endpoints:
 - i. Area under the glucose infusion rate curve in the indicated time-intervals ($AUC_{GIR,0-12h}$, $AUC_{GIR,12-24h}$).
 - ii. Time to maximum glucose infusion rate ($t_{max,GIR}$).
2. To assess the safety and tolerability of MYL-1501D (Process V), MYL-1501D (Process VI), and of US Lantus (insulin glargine injection) as assessed by:
 - a. Adverse events (AEs).
 - b. Local tolerability.
 - c. Laboratory safety parameters.

- d. Physical examination.
- e. Vital signs.
- f. Electrocardiograms (ECGs).

Methodology

This was a Phase 1 randomized, double-blind, single-dose, three-treatment, six period, six sequence, fully replicated, euglycemic glucose clamp study in healthy subjects. The PK, PD, and safety of the long-acting insulin glargine analog MYL-1501D (Mylan GmbH) produced using two different manufacturing processes (Process V and Process VI) were compared to the long-acting insulin analog, US Lantus (insulin glargine injection), which was the reference product. The study consisted of eight study visits: a Screening Visit (Visit 1), six Dosing Periods (Visits 2-7) during the Treatment Period, and a Follow-up Visit (Visit 8). There was a 5-14-day Washout Period between each of the Dosing Periods. Each Dosing Period included one euglycemic glucose clamp and was identical in procedure. PK, PD, and safety endpoints were assessed.

Number of Subjects (planned and analyzed)

The study planned to randomize 84 subjects to ensure that approximately 72 subjects completed the study. Subjects were evenly allocated to one out of six sequences of two replicate single dose administrations for each of the three study products. As a few subjects discontinued from the study and a few had partial data, additional subjects were randomized to ensure an appropriate number of subjects completed all six Dosing Periods. Therefore, a total of 95 subjects were randomized, and 74 subjects (77.9%) completed the study.

Main Criteria for Inclusion and ExclusionInclusion criteria

Subjects who met all the following inclusion criteria were eligible to participate in this study:

1. Signed and dated informed consent obtained before any study-related activities. Study-related activities were any procedures that would not have been performed during normal management of the subject.
2. Healthy male or female subject.
3. Age between 18 and 65 years, both inclusive.
4. Body mass index (BMI) between 18.5 and 29.9 kg/m², both inclusive.
5. Fasting plasma glucose < 100 mg/dL (5.5 mmol/L).
6. Considered generally healthy upon completion of medical history and screening safety assessments as judged by the Investigator, and with no expectation to undergo a medical intervention during the study duration (Note: Out of range laboratory and ECG values were exclusionary only if clinically significant).

Exclusion criteria

Subjects who met any of the following criteria were excluded from participating in the study:

1. Known or suspected hypersensitivity to the study products or related products.
2. Previous participation in this study. Participation was defined as randomized.

3. Receipt of any medicinal product in clinical development within 30 days or 5 half-lives (whichever is longer) before randomization in this study.
4. History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction.
5. Increased risk of thrombosis, (e.g. subjects with a history of deep leg vein thrombosis or family history of deep leg vein thrombosis) as judged by the Investigator.
6. Significant history of alcoholism or drug abuse within the last five years as judged by the Investigator or consuming more than 24 grams of alcohol per day (for males), 12 grams (for females) on average.
7. A positive result in the alcohol and/or urine drug screen.
8. Not able or willing to refrain from smoking and using nicotine substitute products from 24 hours before study product administration until the end of the inpatient period during each visit.
9. Tested positive for hepatitis B surface antigen, hepatitis C antibodies, or human immunodeficiency virus (HIV)-1/2 antibodies or HIV-1 antigen.
10. Used any medication (prescription and non-prescription drugs) within 14 days before study product administration with the exception of hormonal contraception. Paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) for occasional use to treat pain were allowed.
11. Blood donation or blood loss of more than 500 mL within the last 56 days.
12. Mental incapacity, unwillingness, or language barriers precluding adequate understanding or cooperation.
13. Females of childbearing potential who were pregnant, breast-feeding, or intended to become pregnant or were not using highly effective contraceptive methods. Highly effective contraceptive methods were considered those with a failure rate of less than 1% undesired pregnancies per year, including surgical sterilization, hormonal intrauterine devices (coil), oral hormonal contraceptives (to be taken at least 1 month prior to screening), sexual abstinence, or a surgically sterilized partner.
 - a. Women of childbearing potential must have had a negative serum beta human chorionic gonadotropin (β -HCG) pregnancy test performed at Screening.
 - b. Women were not considered of childbearing potential if one of the following was reported and documented on the medical history:
 - i. Postmenopausal with spontaneous amenorrhea for at least one year, or spontaneous amenorrhea for less than one year with serum follicle stimulating hormone (FSH) levels >40 m IU/mL, or

- ii. Bilateral oophorectomy with or without a hysterectomy and an absence of bleeding for at least 6 months, or
- iii. Total hysterectomy and an absence of bleeding for at least 3 months.

Test Product, Dose, Mode of Administration, Lot Number

MYL-1501D (Process V) was administered subcutaneously by an appropriately trained person using a disposable syringe. The dose was 0.5 U/kg on each dosing day, based on the body weight measured prior to each dosing during Visits 2-7. A single lot of MYL-1501D (Process V) insulin glargine solution (BM17002222, exp. 31-Oct2018) was used in this study. Administration of MYL-1501D (Process VI) was identical to MYL-1501D (Process V). A single lot of MYL-1501D (Process VI) insulin glargine solution (BM17002194, exp. 30-Sept-18) was used in this study.

Reference Therapy Dose, Mode of Administration, Lot Number

US Lantus (insulin glargine injection) was administered as the reference drug by an appropriately trained person using a disposable syringe as described for MYL-1501D (Process V) and MYL-1501D (Process VI). The dose was 0.5 U/kg on each dosing day, based on the body weight measured prior to each dosing during Visits 2-7. US Lantus (insulin glargine injection) was not modified from its commercially available form. The Lantus FDA package was used as documentation of the reference product's characterization and was used in lieu of a certificate of analysis.

Statistical Methods**Planned**

This study was to include the following planned analysis populations:

- Full Analysis Set-The Full Analysis Set (FAS) was to be based on the intention-to-treat principle and include all randomized subjects.
- Per Protocol Population - the Per-Protocol-Population (PPP) was to include all subjects in the FAS who completed at least 2 periods of the study without any major protocol deviation. Subjects in the PPP were to contribute to the evaluation 'as treated'.
- Safety Analysis Set - the Safety Analysis Set was to include all subjects receiving at least one dose of study product. Subjects in the safety set were to contribute to the evaluation 'as treated'. The analysis of the safety endpoints was to be based on the Safety Analysis Set.
- PK/PD Analysis Set - all subjects in the PPP were to be included in the PK/PD analysis set, if there were at least two periods of valid PK or PD parameters. If the overall mean clamp coefficient of variation (CV) or the overall mean clamp deviation from target (DFT) for a subject was $\geq 10\%$, based on clamps evaluated for the subject, the subject was to be excluded from the PD analysis set.

Primary PK and PD endpoint analyses

There were to be a total of three pairwise comparisons: MYL-1501D (Process VI) vs. MYL-1501D (Process V), and MYL-1501D (Process V) vs. US Lantus (insulin glargine injection), and MYL-1501D (Process VI) vs. US Lantus (insulin glargine injection). For each pairwise comparison the following analyses method was to be followed:

The primary PK and PD endpoints, $AUC_{GIR,0-24h}$, GIR_{max} , C_{max} , and AUC_{0-24h} data were to be logarithmically transformed since these parameters were assumed to follow a log-normal distribution. Subjects who did not provide evaluable data for four treatment periods were not to be included in the $\mu_T - \mu_R$ related calculation. Subjects who did not provide evaluable data for both periods of reference comparison treatment were not to be included in the σ^2_{WR} related calculation.

- If the intra-subject variability was $\geq 30\%$ for any of the PK or PD parameters for the reference product, then assessment of bioequivalence for that PK or PD parameter was to be performed using the methods described in [Haidar 2008](#), where the parameter(s) was to be evaluated by testing the following null hypothesis:
 - $H_0: ((\mu_T - \mu_R)^2 / \sigma^2_{WR}) > \theta$, where μ_T and μ_R were to be the averages of the log-transformed measure for the test and reference products, respectively, σ_{WR} was to be the intra-subject variability for the reference product; testing was to be done at upper limit at $\alpha=0.05$; and θ was to be the scaled average bioequivalence limit. Furthermore, $\theta = (\ln \Delta)^2 / \sigma^2_{W0}$, where Δ was to be 1.25, the usual average bioequivalence upper limit for the untransformed test/reference ratio of geometric means, and $\sigma_{W0} = 0.25$.
 - Bioequivalence was to be determined for those PK or PD parameters if,
 - A 95% upper confidence bound for $((\mu_T - \mu_R)^2 / \sigma^2_{WR})$ was $\leq \theta$, or equivalently, a 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta \sigma^2_{WR}$ was ≤ 0 , and
 - The point estimate (test/reference geometric mean ratio) fell within 0.80 and 1.25 inclusively.

The programming detail for scaled average bioequivalence analysis followed FDA guidance ([FDA 2011](#)).

- If the intra-subject variability was $< 30\%$ for any of the PK or PD parameters for the reference product, a typical bioequivalence statistical approach was to be applied wherein, ninety (90%) percent CIs were to be constructed, and if the exponentially transformed 90% CI of the LS mean ratio fell within the limits of 80% – 125%, PK or PD bioequivalence were to be demonstrated. The bioequivalence analysis for endpoints with intra-subject variability $< 30\%$ was to use a mixed-effects model with treatment (3 levels), sequence (6 levels) and period (6 periods) as fixed effects. FA0(2) matrix ([FDA 2001](#)) was to model the correlation between different treatments within the same subject via the RANDOM statement in SAS PROC MIXED. A REPEATED statement in SAS PROC MIXED was to estimate separate within subject variances for each treatment. If the model failed to converge, a simpler covariance structure, such as a heterogeneous-compound symmetry or compound symmetric model, was to be used.

The geometric LS mean and the associated geometric 95% CIs for each treatment were to be calculated. In addition, the intra-subject variability CV% was to be calculated for each treatment group. The geometric LS mean ratios and the associated geometric 90% CIs were to be calculated

for MYL-1501D (Process V) and MYL-1501D (Process VI) with US Lantus (insulin glargine injection) as the reference. If intra subject variability in reference treatment was <30% and 90% CI of the LS mean ratio fell within 80%-125%, then PK or PD bioequivalence was to be demonstrated.

If intra subject variability in the reference treatment was $\geq 30\%$ and the 95% upper confidence bound $(\mu_T - \mu_R)^2 - \theta \sigma^2_{WR} \leq 0$, where $\theta = (\ln \Delta)^2 / \sigma^2_{W0} = [\ln(1.25)/0.25]^2 = 0.797$, and the point estimate of the geometric LS mean ratio was between 0.8 and 1.25, then PK or PD bioequivalence was to be demonstrated.

Secondary PK and PD endpoint analyses

The secondary PK/PD endpoints AUC_{0-12h} , AUC_{12-24h} , $AUC_{0-\infty}$, $AUC_{GIR,0-12h}$, $AUC_{GIR,12-24h}$ were to be analyzed using the same statistical approach as for the primary PK/PD endpoints as supportive analysis.

The secondary PK/PD endpoints t_{max} , $t_{1/2}$, λ_z , $t_{max,GIR}$ and C-peptide were to be summarized by descriptive statistics. Individual and mean C-peptide level versus time were to be plotted by treatment and visit.

Sensitivity analyses

The following experiments were to be excluded from the PD-assessments ($AUC_{GIR,0-24}$ and GIR_{max}) in sensitivity analyses:

- Clamps with a pre-clamp C-peptide concentration up to 0.5 nmol/l (median of the values at $t = -30$ min, -15 min and 0 min) may have been excluded if post-dosing C-peptide concentrations increased to 1 nmol/L or higher during the experiment.
- Clamps with a pre-clamp C-peptide concentration above 0.5 nmol/L may have been excluded if post-dosing C-peptide concentrations increased to at least 100% of baseline values during the experiment.

Three sensitivity analyses were to be performed. The first one was to exclude all subject PD data that met the above two criteria during that Treatment Period; the second one was to exclude all subject PD data that met the criteria in last 12 hours during that Treatment Period; the third one was to exclude all subject PD data that met the criteria only in the first 12 hours during that Treatment Period.

Safety endpoint analyses

AEs were to be summarized using the Safety Analysis Set. All reported terms (Investigator descriptions) for AEs were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1. Number and percentage of subjects with treatment emergent AEs (TEAEs), defined as those that onset or worsened after the first dose of study product, were to be summarized by system organ class and preferred term. AEs that occurred prior to receiving study product were not to be summarized but were to be provided in listings. Number and percentage of subjects with TEAEs leading to study discontinuation, TEAEs relationship to study product, SAEs, and TEAE by maximum severity were to be summarized.

Severe hypoglycemia, documented symptomatic hypoglycemia, and asymptomatic hypoglycemia were to be fully reported and listed in the listing. All hematology, biochemistry, coagulation, urinalysis, infectious serology, and other serum lab assessments were to be listed, including scheduled and unscheduled/repeat measurements. Baseline values, the values at each scheduled post-baseline visit, and changes from the baseline values were to be summarized descriptively for each of the quantitative laboratory assessments. Shift tables of hematology and clinical chemistry were to summarize the normal and abnormal (abnormal high and abnormal low) status changes from baseline visit to post-baseline visits. All lab results and comments were to be listed. Laboratory assessments that were outside of normal ranges were to be summarized and flagged in the listings. Vital signs were to be summarized with descriptive statistics by treatment and time point. ECG data at Screening, pre- and post-clamp, and at Follow-Up were to be summarized with descriptive statistics. Qualitative ECG data at Screening, pre- and post-clamp, and at Follow-Up were to be summarized categorically. Abnormal individual evaluations were to be listed together with the Investigator's comments. Physical examination findings were to be summarized categorically by body system. Local tolerability was to be summarized by descriptive statistics by treatment/time point.

Results Summary

Subject Disposition

A total of 95 subjects were randomized, and 74 subjects (77.9%) completed the study. A total of 21 subjects did not complete the study; nine (9) subjects withdrew due to 'voluntary withdrawal of consent', and an additional nine (9) subjects withdrew due to 'discretion of the investigator'. Among the subjects that voluntarily withdrew consent, Subjects (b) (6) provided no reason; Subjects (b) (6) no longer wished to participate; and Subject (b) (6) experienced chest pain, which resolved on (b) (6). An ECG that was conducted on (b) (6) was classified as abnormal but not clinically significant (NCS). Among subjects that were discontinued at the discretion of the Investigator, Subjects (b) (6) were unable to commit to study dates; Subject (b) (6) did not have good venous access for the clamp; and Subject (b) (6) experienced anxiety caused by alcohol withdrawal and did not wish to return for the Follow-Up visit (Visit 8). Other reasons for withdrawal included 'protocol deviation' (n=1, 1.1%); 'pregnant or breastfeeding' (n=1, 1.1%); and 'other' (n=1, 1.1%).

All of the enrolled subjects, 95 subjects, were included in the FAS and the Safety Analysis Set. Seven subjects were excluded from the PPP, 88 subjects, which included all subjects in the FAS who completed at least 2 periods of the study without any major protocol deviation. All subjects in the PPP were included in the PK analysis set. One subject in the PPP was excluded from the PD analysis set as the overall mean clamp CV was 10. For the PD analysis set, subjects with an overall mean clamp CV or overall mean clamp DFT $\geq 10\%$ were excluded. Due to poor quality of clamps data for subjects (b) (6) the following procedure was implemented for PK/PD analysis:

- For Subject (b) (6) the overall mean clamp CV was 10, and hence data were excluded from the PD analysis set. However, this subject's PK data were used in the PK analysis.
- For Subject (b) (6), PD data in Dosing Periods 1 and 7 were not used for PD analysis (this subject was dosed 7 times, as the subject underwent a repeat clamp on Dosing Period 7 for

Dosing Period 1). PK data in Dosing Period 1 were used for PK analysis, and PK data in Dosing Period 7 were not used for PK analysis.

- For Subject (b) (6) Dosing Period 4, PD data were not used for PD analysis, but PK data were used for PK analysis.
- For Subject (b) (6) PD data in Dosing Period 5 were not used for PD analysis, but PK data were used for PK analysis.

The subjects listed below were excluded from the primary statistical analysis as a priori per Statistical Analysis Plan and protocol:

- Subjects with pre-dose concentrations greater than 5% C_{max}
 - Subject (b) (6) Period 2
 - Subject (b) (6) Period 3

The subjects listed below were excluded from the primary statistical analysis and documented before randomization unblinding (Note-to-file, 9 Nov 2018):

- Subjects with anomalous spikes in M1 concentrations within 2 hours after dosing; possibly indicative of dose injection into a vein as opposed to protocol-required subcutaneous injection:
 - Subject (b) (6) Period 2
 - Subject (b) (6) Period 1

Please note: the same subject (b) (6) at Period 2 was included in both cases, so a total of three subject-periods that were excluded from the PK primary analysis:

- Subject (b) (6) Period 2
- Subject (b) (6) Period 1
- Subject (b) (6) Period 3

Demographics and Baseline Characteristics

The demographic and baseline characteristics of the subjects were well balanced between the treatment sequences. The mean ($\pm$ SD) age for the subjects was 40.1 ($\pm$ 11.07) years, most subjects were male (n=65, 68.4%). The subjects identified predominantly as White (n=58, 61.1%) and Black or African American (n=26, 27.4%), and Hispanic or Latino (n=34, 35.8%). Mean ($\pm$ SD) BMI at Screening was 26.23 ($\pm$ 2.562) kg/m².

PK Analyses

Primary Pharmacokinetic Endpoints – Insulin Glargine M1 AUC_{0-24h} and C_{max}

For plasma insulin glargine M1 AUC_{0-24h} and C_{max}, determination of bioequivalence was based on the 90% CI of the LS mean ratio falling within prespecified limits (80% to 125%), as intra subject variabilities were <30% for the reference treatment. These primary PK analyses indicate that MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) are bioequivalent in terms of the plasma insulin glargine M1 AUC_{0-24h} and C_{max} parameters

For plasma insulin glargine M1 AUC_{0-24h} , intra subject variability was 22.8% for MYL-1501D (Process V), 21.8% for MYL-1501D (Process VI), and 21.31% for US Lantus. The 90% CI of the LS mean ratio was 98.91% to 107.28% for MYL-1501D (Process VI) vs. MYL-1501D (Process V), 92.56% to 99.97% for MYL-1501D (Process V) vs. US Lantus, and 95.11% to 103.22% for MYL-1501D (Process VI) vs. US Lantus.

For plasma insulin glargine M1 C_{max} , intra subject variability was 25.56% for MYL-1501D (Process V), 25.19% for MYL-1501D (Process VI), and 22.55% for US Lantus. The 90% CI of the LS mean ratio was 98.07% to 107.52% for MYL-1501D (Process VI) vs. MYL-1501D (Process V), 93.01% to 101.37% for MYL-1501D (Process V) vs. US Lantus, and 95.30% to 104.33% for MYL-1501D (Process VI) vs. US Lantus.

Secondary Pharmacokinetic Endpoints – AUC_{0-12h} , AUC_{12-24h} , AUC_{0-inf} , T_{max} , λ_z , and $\ln 2/\lambda_z$

For plasma insulin glargine M1 AUC_{0-12h} , AUC_{12-24h} , and AUC_{0-inf} , determination of bioequivalence was based on the 90% CI of the LS mean ratio falling within prespecified limits (80% to 125%), as intra subject variabilities were <30% for the reference treatment; for plasma insulin glargine M1 AUC_{0-inf} , intra subject variability was 30.07% for the reference treatment. These secondary PK analyses indicate that MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) are bioequivalent in terms of the plasma insulin glargine M1 AUC_{0-12h} , AUC_{12-24h} , and AUC_{0-inf} parameters. Descriptive analyses showed no obvious differences in the plasma insulin glargine M1 T_{max} , λ_z , and $\ln 2/\lambda_z$ parameters.

Sensitivity Analysis of PK Parameters

Sensitivity analysis of the PK parameters was performed by including data from Subject (b) (6) Period 2, (b) (6) Period 1, and (b) (6) Period 3 who were excluded from the primary analyses due to either pre-dose concentration > 5% C_{max} or having anomalous spikes in M1 concentrations within 2 hours after dosing. For the sensitivity analysis of PK parameters, determinations of bioequivalence were based on the 90% CI of the LS mean ratio falling within prespecified limits (80% to 125%), as intra subject variabilities were <30% for the reference treatment; for plasma insulin glargine M1 AUC_{0-inf} , intra subject variability was 30.07% for the reference treatment. The sensitivity analysis supported bioequivalence between MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) in terms of the primary and secondary PK parameters of plasma insulin glargine M1 concentrations.

Primary Pharmacodynamic Endpoints – $AUC_{GIR,0-24h}$ and GIR_{max}

For $AUC_{GIR,0-24h}$ and GIR_{max} , determinations of bioequivalence were based on a 95% upper CI ≤ 0 , and the point estimate of the geometric LS mean ratio falling within prespecified limits (80% to 125%), as intra subject variabilities were $\geq 30\%$ for the reference treatment. These primary PD analyses indicate that MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) are bioequivalent in terms of the $AUC_{GIR,0-24h}$ and GIR_{max} parameters.

For $AUC_{GIR,0-24h}$, intra subject variability was 49.67% for MYL-1501D (Process V), 40.42% for MYL-1501D (Process VI), and 42.95% for US Lantus. The 95% upper CI and point estimate of the geometric LS mean ratio were -1.462 and 106.05% for MYL-1501D (Process VI) vs. MYL-1501D (Process V), -1.025 and 92.25% for MYL-1501D (Process V) vs. US Lantus, and -1.129 and 98.05% for MYL-1501D (Process VI) vs. US Lantus.

For GIR_{max} , intra subject variability was 38.01% for MYL-1501D (Process V), 31.76% for MYL-1501D (Process VI), and 36.34% for US Lantus. The 95% upper CI and point estimate of the geometric LS mean ratio were -.0864 and 103.89% for MYL-1501D (Process VI) vs. MYL-1501D (Process V), -.0791 and 96.21% for MYL-1501D (Process V) vs. US Lantus, and -.0819 and 99.56% for MYL-1501D (Process VI) vs. US Lantus.

Secondary Pharmacodynamic Endpoints – $AUC_{GIR,0-12h}$, $AUC_{GIR,12-24h}$, and $T_{max,GIR}$

For $AUC_{GIR,0-12h}$ and $AUC_{GIR,12-24h}$, determinations of bioequivalence were based on a 95% upper CI ≤ 0 , and the point estimate of the geometric LS mean ratio falling within prespecified limits (80% to 125%), as intra subject variabilities were $\geq 30\%$ for the reference treatments. These secondary PD analyses indicate that MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) are bioequivalent in terms of the $AUC_{GIR,0-12h}$ and $AUC_{GIR,12-24h}$ parameters. Descriptive analyses showed no obvious differences in the $T_{max,GIR}$ parameter.

Sensitivity Analysis of Pharmacodynamic Parameters

Sensitivity analyses of the primary and secondary PD endpoints were performed with a clamp CV and DFT constraint, and C-peptide constraints. For the clamp CV and DFT constraint, if the calculated clamp CV for an individual clamp was $\geq 12\%$ or clamp DFT was $\geq 12\%$, the subject clamp profile was excluded from the analysis. For the C-peptide constraints, clamps with a pre-clamp C-peptide concentration up to 0.5 nmol/l were excluded if post-dosing C-peptide concentrations increased ≥ 1 nmol/L during the experiment. Clamps with a pre-clamp C-peptide concentration >0.5 nmol/L were excluded if post-dosing C-peptide concentrations increased to at least 100% of baseline values during the experiment. For the C-peptide constraints, three sensitivity analyses were performed. The first one excluded all subject PD data that met the above two criteria during that Treatment Period; the second one excluded all subject PD data that met the criteria in the last 12 hours during that Treatment Period; the third one excluded all subject PD data that met the criteria only in the first 12 hours during that Treatment Period. For sensitivity analyses of PD parameters, determinations of bioequivalence were based on a 95% upper CI ≤ 0 , and the point estimate of the geometric LS mean ratio falling within prespecified limits (80% to 125%), as intra subject variabilities were $\geq 30\%$ for the reference treatments. These sensitivity analyses supported bioequivalence of MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) in terms of the $AUC_{GIR,0-24h}$, GIR_{max} , $AUC_{GIR,0-12h}$, and $AUC_{GIR,12-24h}$ parameters.

Safety Analyses

The number of reported TEAEs was low and similar between MYL5105D (Process V), MYL5105D (Process VI), and US Lantus (insulin glargine injection). All the reported TEAEs were mild or moderate in nature, there were no severe TEAEs. Gastrointestinal disturbance, infusion site discomfort, and nervous system disorders were the most frequently reported TEAEs. No subjects who withdrew from the study experienced a TEAE related to the study drug, as assessed by the Investigator. There were no clinically meaningful changes in clinical laboratory evaluations, or vital signs, 12-lead ECG, physical examination, or local tolerability assessments. Overall, MYL-1501D (Process V), MYL-1501D (Process VI) and US Lantus (insulin glargine injection) were well tolerated and safe.

Conclusions

PK and PD Conclusions

- For PK parameters, determination of bioequivalence was based on the 90% CI of the LS mean ratio falling within prespecified limits (80% to 125%), as intra subject variabilities were <30% for the reference treatment; for plasma insulin glargine M1 AUC_{0-inf}, intra subject variability was 30.07% for the reference treatment.
- The results demonstrate MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) are bioequivalent in terms of the plasma insulin glargine M1 AUC_{0-24h}, C_{max}, AUC_{0-12h}, AUC_{12-24h}, and AUC_{0-inf} parameters.
- The PK parameters are comparable between MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection).
- The results of the sensitivity analysis that included Subject (b) (6) Period 2, (b) (6) Period 1, and (b) (6) Period 3 who were excluded from the primary analyses due to either pre-dose concentration > 5% C_{max} or having anomalous spikes in M1 concentrations within 2 hours after dosing supported bioequivalence between MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection).
- For PD parameters, determinations of bioequivalence were based on a 95% upper CI ≤ 0, and the point estimate of the geometric LS mean ratio falling within prespecified limits (80% to 125%), as intra subject variabilities were ≥30% for the reference treatment.
- The results demonstrate MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection) are bioequivalent in terms of the AUC_{GIR,0-24h}, GIR_{max}, AUC_{GIR,0-12h}, and AUC_{GIR,12-24h} parameters.
- The PD parameters are comparable between MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection).
- The results of the sensitivity analyses performed using a clamp CV and DFT constraint, and C-peptide constraints supported bioequivalence between MYL-1501D (Process V), MYL-1501D (Process VI), and US Lantus (insulin glargine injection).

Safety Conclusions

- There were no deaths or SAEs in this study.
- The number of reported TEAEs was similar between MYL5105D (Process V), MYL5105D (Process VI), and US Lantus (insulin glargine injection).
- All the reported TEAEs were mild or moderate in nature.
- Gastrointestinal disturbance, infusion site discomfort, and nervous system disorders were the most frequently reported TEAEs.
- No subjects who withdrew from the study experienced a TEAE related to the study drug, as assessed by the Investigator.
- There were no clinically meaningful changes in clinical laboratory evaluations, or vital signs, 12-lead ECG, physical examination, or local tolerability assessments.

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/

JING NIU
07/25/2019 04:15:39 PM

MANOJ KHURANA
07/25/2019 04:20:04 PM

ADDENDUM OF CLINICAL PHARMACOLOGY REVIEW

NDA	210605 Serials 0000
Submission Dates	April 27, 2017, September 15, 2017 (file over protest)
Brand Name	Semglee
Generic Name	Insulin glargine (MYL-1501D)
Reviewer	Jing Niu, M.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Mylan GmbH
Formulation; Strength; Presentation	Solution for subcutaneous injection; 100 units/mL; 10 mL vial and 3mL cartridge
Relevant IND	105279
Indication	Long-acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus

This memo provides clarification to the following Clinical Pharmacology recommendations in the original Clinical Pharmacology review of the application finalized on April 24, 2018 for NDA 210605:

“OCP finds the submitted clinical pharmacology data is acceptable to support the approval of NDA 210605, pending the resolution of clinical safety concerns arising from the change in formulation from MIG-V to MIG-VI, and CMC assessment of the claims that MIG-VI is improvised version of MIG-V product from a purity perspective.”

The above recommendation only applies to the “cartridge presentation” of MYL-1501D formulation. The clinical pharmacology review dated April 24, 2018 conveyed the already raised concern over the lack of bridging study between the proposed cartridge and vial presentations of the product needed for approval of the vial presentation. The sponsor was made aware of this during the face-to-face post-refuse to file meeting on August 15, 2017. A study to address this concern has already been planned by the sponsor after filing the NDA over protest. The lack of bridging study between cartridge and vial presentations of the product needs to be included as a deficiency in the application for one of the presentations.

The revised OCP recommendation is as follows:

“OCP finds the submitted clinical pharmacology data is acceptable to support the approval of NDA 210605 as it pertains to the cartridge presentation of MYL-1501D formulation, pending the resolution of clinical safety concerns arising from the change in formulation

from MIG-V to MIG-VI, and CMC assessment of the claims that MIG-VI is improvised version of MIG-V product from a purity perspective, and submission of the adequate bridging data between vial and cartridge presentations deemed necessary for the approval of the vial presentation.”

The following needs to be communicated to the sponsor as the OCP Recommendation:

You have not submitted the bridging data necessary for approval of the vial presentation of your product. The recommendation regarding the need for additional PK/PD comparability study between your cartridge and vial presentations was also conveyed during the Type A meeting held on Aug 15, 2017. Submit the results from the proposed study (Study MYL-1501D-1004) to address this deficiency.

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

/s/

JING NIU
05/14/2018

MANOJ KHURANA
05/14/2018

CLINICAL PHARMACOLOGY REVIEW

NDA	210605 Serials 0000
Submission Dates	April 27, 2017, September 15, 2017 (file over protest)
Brand Name	Semglee
Generic Name	Insulin glargine (MYL-1501D)
Reviewer	Jing Niu, M.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Mylan GmbH
Formulation; Strength; Presentation	Solution for subcutaneous injection; 100 units/mL; 10 mL vial and 3mL cartridge
Relevant IND	105279
Indication	Long-acting human insulin analog indicated to improve glycemic control in adults and children with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus

Table of Contents

1 Executive Summary	2
1.1 Recommendations	2
1.2 Post Marketing Requirement	3
1.3 Summary of Important Clinical Pharmacology Findings	3
2 Question-Based Review	5
2.1 General Attributes	5
2.2 Key Clinical Pharmacology Questions	7
2.3 Bioanalytical	17
3 Preliminary Labeling Recommendations	20
4 Appendix: Synopsis of Study MYL-1501D-1001	21

1 Executive Summary

The sponsor submitted NDA 210605 via the 505(b)(2) regulatory pathway to seek approval of subcutaneous (SC) administration of Semglee (MYL-1501D) indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. The sponsor is relying upon the Agency's previous findings of safety and effectiveness for the reference listed drug (RLD), Lantus® (Insulin Glargine Recombinant; NDA 021081, Sanofi Aventis US). Semglee is proposed as a 100 units/mL solution of MYL-1501D for SC injection, and will be made available in 10 mL vial presentation as well as 3 mL cartridge sealed in a prefilled pen injector.

Clinical pharmacology of MYL-1501D under this 505(b)(2) submission was supported by four clinical studies including two PKPD similarity studies (MYL-1501D-1001 and GLARGCT100111). In addition, the sponsor conducted two randomized, open-label, active-controlled, parallel-group, non-inferiority Phase 3 trials in patients with type 1 diabetes (T1DM; MYL-GAI-3001) and type 2 diabetes (T2DM; MYL-GAI-3002) to assess the relative efficacy and safety of MYL-1501D compared to Lantus. The PKPD similarity study (MYL-1501D-1001) was deemed pivotal for approval from a clinical pharmacology perspective.

For simplicity, this review refers the following:

- MIG-VI for the sponsor's insulin glargine manufactured using Process VI at a facility in Malaysia. MIG-IV is the to-be-marketed insulin glargine product.
- MIG-V for the sponsor's insulin glargine manufactured using Process V at a facility in India. MIG-V is the product used in the Phase 3 studies.
- US-Lantus for listed drug, insulin glargine approved and marketed in the United States under NDA 021081
- EU-Lantus for insulin glargine approved and marketed in the European Union

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the clinical pharmacology data submitted under NDA 210605 and has following recommendations:

- The pivotal Study MYL-1501D-1001 results are acceptable to establish pharmacokinetic and pharmacodynamic (PK/PD) similarity between intended commercial formulation MIG-VI and US-Lantus for the 3 mL cartridge presentation and bridging the intended commercial formulation (MIG-VI) and the Phase 3 formulation (MIG-V) from efficacy perspective. The study results could not establish the PD similarity between MIG-V and US-Lantus.
- Although, sponsor is not seeking the approval of MIG-V formulation, the supportive Study GLARGCT100111 results are acceptable to establish PK/PD similarity between MIG-V and US-Lantus, as well as the similarity between US-Lantus and EU-Lantus. The study specific differences may have led to variations in the results as these two studies reportedly followed different euglycemic clamp technology.
- Totality of evidence points to a lack of clinical relevance of the PD differences observed between MIG-V and US-Lantus in Study MYL-1501D-1001, and there is supportive

evidence from Study GLARGCT100111, which showed PK/PD similarity between MIG-V and US-Lantus.

- Overall, OCP finds the submitted clinical pharmacology data is acceptable to support the approval of NDA 210605, pending the resolution of clinical safety concerns arising from the change in formulation from MIG-V to MIG-VI, and CMC assessment of the claims that MIG-VI is improvised version of MIG-V product from a purity perspective.

1.2 Post Marketing Requirement

None.

1.3 Summary of Important Clinical Pharmacology Findings

The sponsor submitted the following clinical studies to support NDA 210605:

- Study MYL-1501D-1001 to characterize and compare the pharmacokinetics (PK) and pharmacodynamics (PD, namely glucose infusion rate [GIR]) of MIG-V, MIG-VI, and US-Lantus upon single subcutaneous doses of 0.5 unit/kg in a euglycemic clamp study in patients with T1DM
- Study GLARGCT100111 to compare the PK and PD of MIG-V, US-Lantus, and EU-Lantus upon single subcutaneous doses of 0.4 unit/kg in a euglycemic clamp study in patients with T1DM. Study GLARGCT100111 was supportive, as MIG-V is not the to-be-marketed product and the manufacturing change from MIG-V to MIG-VI was deemed a major change
- Study MYL-GAI-3001 to demonstrate non-inferiority of MIG-V versus US-Lantus for change in hemoglobin A1c (HbA1c) from baseline to Week 24 in patients with T1DM also receiving insulin lispro
- Study MYL-GAI-3002 to demonstrate non-inferiority of MIG-V versus US-Lantus for change in hemoglobin A1c (HbA1c) from baseline to Week 24 in patients with T2DM also receiving insulin lispro

Highlights of PK/PD comparisons from Study MYL-1501D-1001:

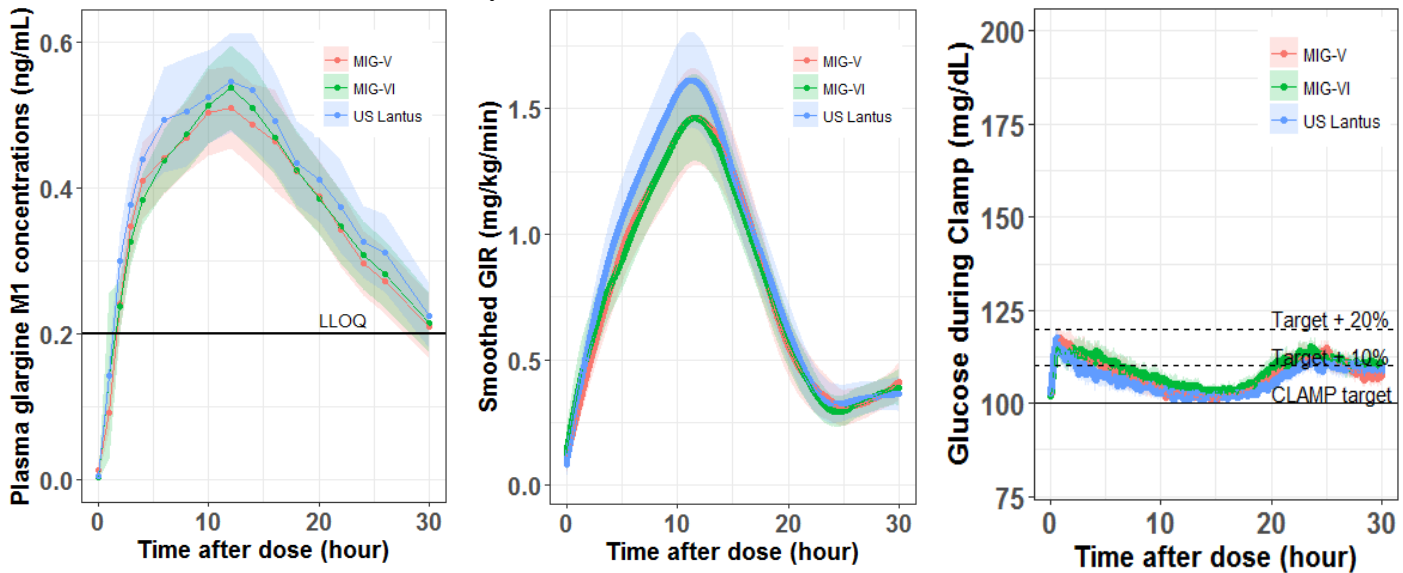
- For the comparison of MIG-VI to US-Lantus, as well as the comparison of MIG-VI to MIG-V, Study MYL-1501D-1001 showed that the geometric mean ratios and 90% confidence interval (CI) for both primary PK ($C_{\max}$ and AUC_{0-24h}) and PD ($GIR_{\max}$ and $AUC_{GIR0-24h}$) parameters were within the prespecified goalpost of 0.80 – 1.25
- For the comparison of MIG-V to US-Lantus, Study MYL-1501D-1001 showed that the geometric mean ratios and 90% confidence interval (CI) for the primary PK ($C_{\max}$ and AUC_{0-24h}) parameters and $GIR_{\max}$ were within the prespecified goalpost of 0.80 – 1.25, however, the $AUC_{GIR0-24h}$ fell slightly below on the lower side of the confidence interval, (78.30%; 98.47%)
- Figure 1 shows the mean (90% CI bands) PK, mean (90% CI bands) smoothed GIR (PD), mean (90% CI bands) glucose profiles of MIG-VI, MIG-V and US-Lantus. Table 1 shows the statistical comparisons of the primary PK and PD parameters for Study MYL-1501D-1001

- Duration of action of MIG-VI was compared to US-Lantus in Study MYL-1501D-1001 at 0.5 unit/kg doses. The median duration of action was 30 hours for MIG-V, MIG-VI, and US-Lantus, based on the pre-defined criteria by the sponsor (time when blood glucose consistently above 150 mg/dL)

In summary, Study MYL-1501D-1001 showed the PK and PD data:

- are similar between intended commercial formulation - MIG-VI and US-Lantus
- are similar between intended commercial formulation MIG-VI and formulation tested in Phase 3 - MIG-V, providing adequate bridging between the two
- are similar between formulation tested in Phase 3 MIG-V and US-Lantus for PK, but the $AUC_{GIR0-24h}$ fell slightly below on the lower side of the confidence interval, (78.30; 98.47)
- Even though the MIG-V is not the intended commercial formulation, from a totality of evidence perspective, the safety/efficacy trial results present the relevance (or lack thereof) of the differences noted in PK/PD study

Figure 1. Mean (90% CI) insulin glargine concentration - time, smoothed glucose infusion rate (GIR) - time, and blood glucose concentration - time plots (single SC dose of 0.5 unit/kg MIG-V, MIG-VI and US-Lantus; Study MYL-1501D-1001).



Source: Reviewer's analysis

Table 1. Statistical analysis results for primary PK and PD parameters

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

Study results from GLARGCT100111 provided additional supportive evidence of PK/PD similarity between MIG-V and US-Lantus and the scientific bridge between US-Lantus and EU-Lantus. In summary, Study GLARGCT100111 showed:

- the primary PK and PD parameters (AUC_{ins.0-30h}, C_{ins.max}, AUC_{GIR.0-30h} and GIR_{max}) are similar between MIG-V and US-Lantus
- the primary PK and PD parameters (AUC_{ins.0-30h}, C_{ins.max}, AUC_{GIR.0-30h} and GIR_{max}) are similar between US-Lantus and EU-Lantus
- the primary PK and PD parameters (AUC_{ins.0-30h}, C_{ins.max}, AUC_{GIR.0-30h} and GIR_{max}) are similar between MIG-V and EU-Lantus

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the formulation of the to-be-marketed MYL-1501D?

Table 2 details the formulation of the to-be-marketed MYL-1501D. As highlighted, (b) (4) 20 µg/mL polysorbate-20, was added to the product formulation of the 10 mL vial presentation. This formulation change is in line with the formulation change between vials and cartridges of the RLD, US-Lantus.

The reviewer note that only the cartridge presentation of MYL-1501D and US-Lantus was compared in study MYL-1501d-1001, MYL-GAI-3001 and MYL-GAI-3002. To support the vial presentation of MYL-1501D, which has a different composition from the cartridge, the reviewer recommended the sponsor to conduct additional PK/PD comparability study between Mylan's cartridge and vial presentation. This recommendation has been conveyed to Mylan in a face-to-face type A meeting in Aug 15 2017. As a result, Mylan submitted a protocol of a two-way PK/PD study to investigate the bioequivalence of MIG-VI in vials versus MIG-VI in cartridges

in healthy volunteers. See the type A meeting minutes and the proposed protocol (study MYL-1501D-1004) in DARRTs for details.

Table 2. The to-be-marketed MYL-1501D insulin glargine solution for injection 100 units/mL.

Presentation	Component	Quantity/mL	Quantity per cartridge/vial	Quality standard	Function
3 mL cartridge	Insulin glargine	100 units ²	300 units ²	In-house	Active ingredient
	m-Cresol	2.7 mg	8.1 mg	USP and Ph. Eur.	(b) (4)
	Glycerol (85% (b) (4))	20 mg	60 mg	Ph. Eur.	(b) (4)
	Zinc ¹ (b) (4)	30 µg	90 µg	USP and Ph. Eur.	(b) (4)
	Hydrochloric acid	q.s.	q.s.	USP and Ph. Eur.	pH adjustment
	Sodium hydroxide	q.s.	q.s.	USP and Ph. Eur.	pH adjustment
	Water for injection	q.s. to 1 mL	q.s. to 3 mL	USP and Ph. Eur.	(b) (4)
10 mL vial	Insulin glargine	100 units ²	1000 units ²	In-house	Active ingredient
	m-Cresol	2.7 mg	27 mg	USP and Ph. Eur.	(b) (4)
	Glycerol (85% (b) (4))	20 mg	200 mg	Ph. Eur.	(b) (4)
	Zinc ¹ (b) (4)	30 µg	300 µg	USP and Ph. Eur.	(b) (4)
	Polysorbate-20	20 µg	200 µg	USP and Ph. Eur.	(b) (4)
	Hydrochloric acid	q.s.	q.s.	USP and Ph. Eur.	pH adjustment
	Sodium hydroxide	q.s.	q.s.	USP and Ph. Eur.	pH adjustment
	Water for injection	q.s. to 1 mL	q.s. to 10 mL	USP and Ph. Eur.	(b) (4)
Ph. Eur: European Pharmacopoeia; q.s.: quantity sufficient; USP: United States Pharmacopeia.					
¹ Zinc quantity is calculated (b) (4) in the drug substance to make the final quantity of zinc 30 µg/100 units of insulin glargine.					
² 100 units of insulin glargine corresponds to 3.64 mg of insulin glargine					

Source: Adjusted from Sponsor's Quality Overall Summary – Table 2.3.P/1.

2.1.2 Is there any difference between the clinically-tested product of MYL-1501D and the to-be-marketed product of MYL-1501D?

The sponsor has submitted NDA210605 for the proposed to-be-marketed insulin glargine product manufactured using Process VI at a facility in Malaysia (i.e., MIG-VI product), while the

insulin glargine product studied in the Phase 3 clinical trials was manufactured using Process V at a different facility in India (i.e., MIG-V product).

The review team consider the manufacturing change to be a major change and requested additional clinical safety and efficacy bridging data, including an assessment of immunogenicity, to establish that the efficacy and safety data generated with MIG-V product (i.e., Phase 3 product) is relevant to MIG-VI product and can be used to support a determination that the proposed to-be-marketed product (i.e., MIG-VI product) is sufficiently similar to US-Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for US-Lantus. See the refusal to file correspondence in June 26 2017 and the type A meeting minutes in Aug 15 2017 in DARRTs for details.

2.2 Key Clinical Pharmacology Questions

2.2.1 What are the design features of Study MYL-1501D-1001?

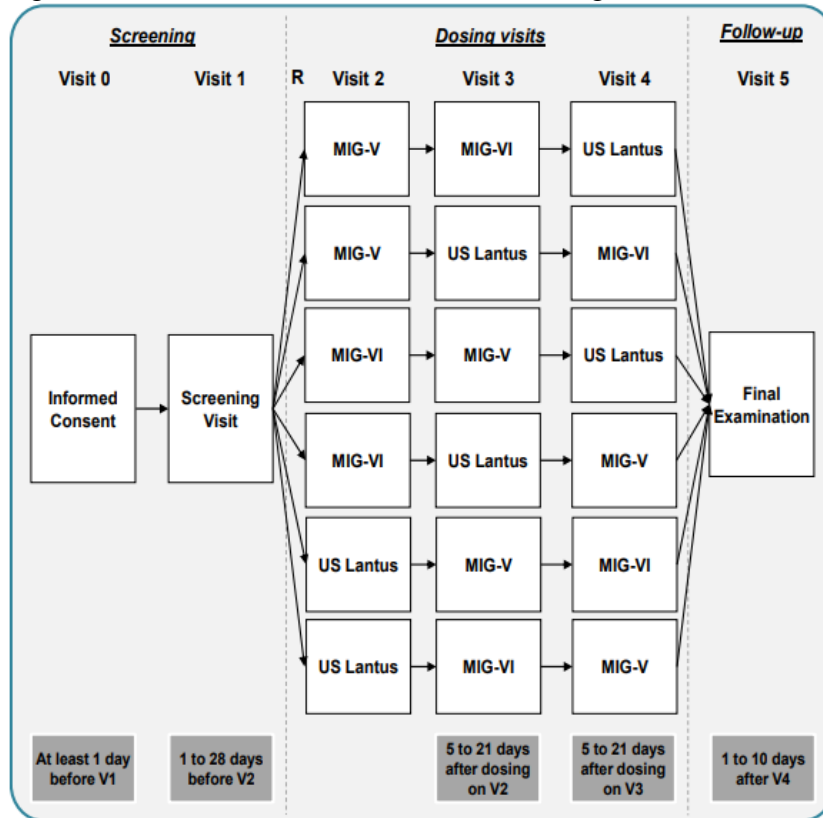
Study MYL-1501D-1001 was a phase 1, two-center, randomized, double-blind, 3-treatment, 3-period crossover trial comparing single doses of 0.5 unit/kg for MIG-V and MIG-VI insulin glargine with US-Lantus in two centers in Germany.

A total of 116 male subjects (age 18-64 years) with Type 1 diabetes were randomized in the study and 113 were completers. Each subject participated in 6 visits (Figure 2): an informed consent visit (at least one day before Visit 1), a screening visit (Visit 1, 1 to 28 days before Visit 2) to check eligibility for participation, three dosing visits (Visits 2, 3 and 4, separated by a washout period of 5 to 21 days), and a follow-up visit with final examination (Visit 6, 1 to 10 days after Visit 4). At Visits 2, 3 and 4, the three insulin products were administered in 6 randomly allocated sequences in the setting of a 30-hour computer-controlled euglycemic glucose clamp (ClampArt; Profil Neuss, Germany). Subjects were connected to the clamp device, which monitored the subjects' blood glucose (BG) continuously. The device calculated an average BG value every minute. Based on this average value, the GIR was calculated every minute using the algorithm implemented into the device, and were administered automatically by the device to keep the subject's BG concentrations constant at a pre-determined target level (100 mg/dL $\pm$ 20%). The device's glucose measurements were verified approximately every 30 minutes or more frequently, if needed, by BG measurements with a laboratory glucose analyzer (Super GL glucose analyzer).

The subjects remained fasting and stayed in a supine or semi-supine position during the entire glucose clamp. Blood was collected pre-dose until 30 hours' post-dose in pre-specified intervals for measurement of BG and insulin glargine metabolite 1 (M1).

Overall, Study MYL-1501D-1001's design was acceptable.

Figure 2. Schematic overview of the chronological structure of Study MYL-1501D-1001



Source: CSR of Study MYL-1501D-1001– Figure 9-1.

2.2.2 Are the PK and PD characteristics of MIG-VI similar to those of US-Lantus? Are the PK and PD characteristics of MIG-VI similar to those of MIG-V? Are the PK and PD characteristics similar between MIG-V and US-Lantus?

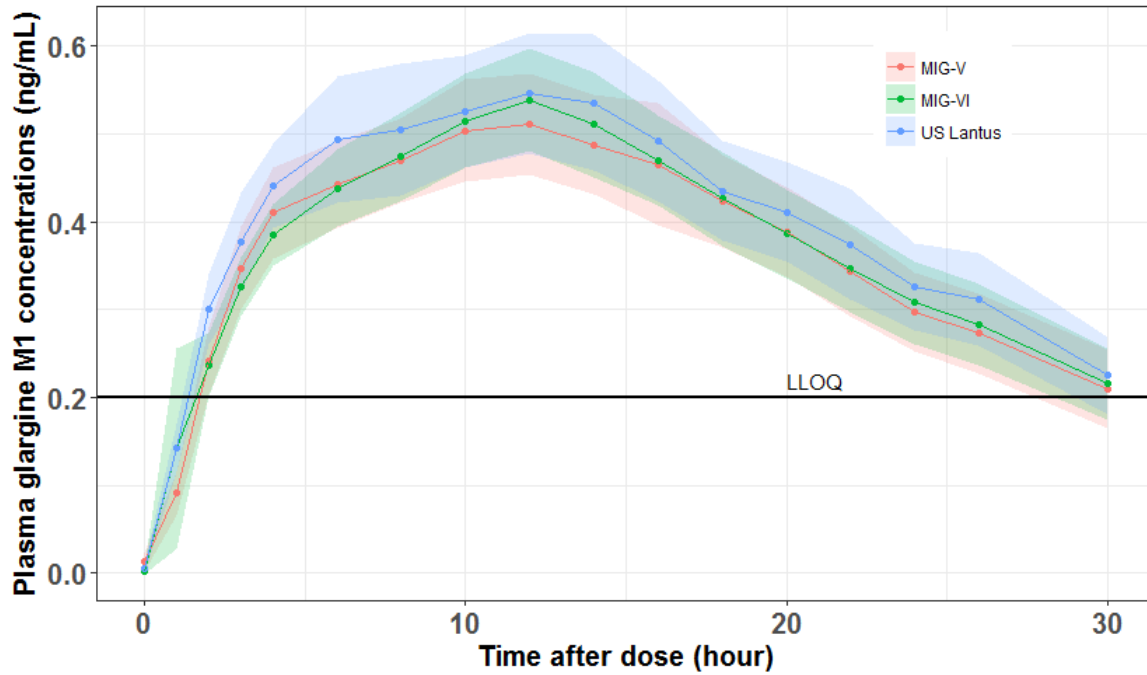
In summary, Study MYL-1501D-1001 showed the PK and PD data:

- are similar between MIG-VI and US-Lantus
- are similar between MIG-VI and MIG-V
- are similar between MIG-V and US-Lantus for PK, but the $AUC_{GIR0-24h}$ fell slightly below on the lower side of the confidence interval, (78.30; 98.47).

Figure 3 shows the mean (90% CI) plasma insulin glargine concentration versus time profiles of single doses of MIG-VI, MIG-V, and US-Lantus in patients with T1DM. Upon SC injection of 0.5 unit/kg, maximum plasma insulin glargine concentrations occurred at about 11 hours post-dose for MIG-VI, MIG-V, and US-Lantus and then decline to about 30 hours near quantitation limit. In general, the mean plasma insulin glargine concentration versus time profiles of MIG-VI, MIG-V, and US-Lantus appear similar.

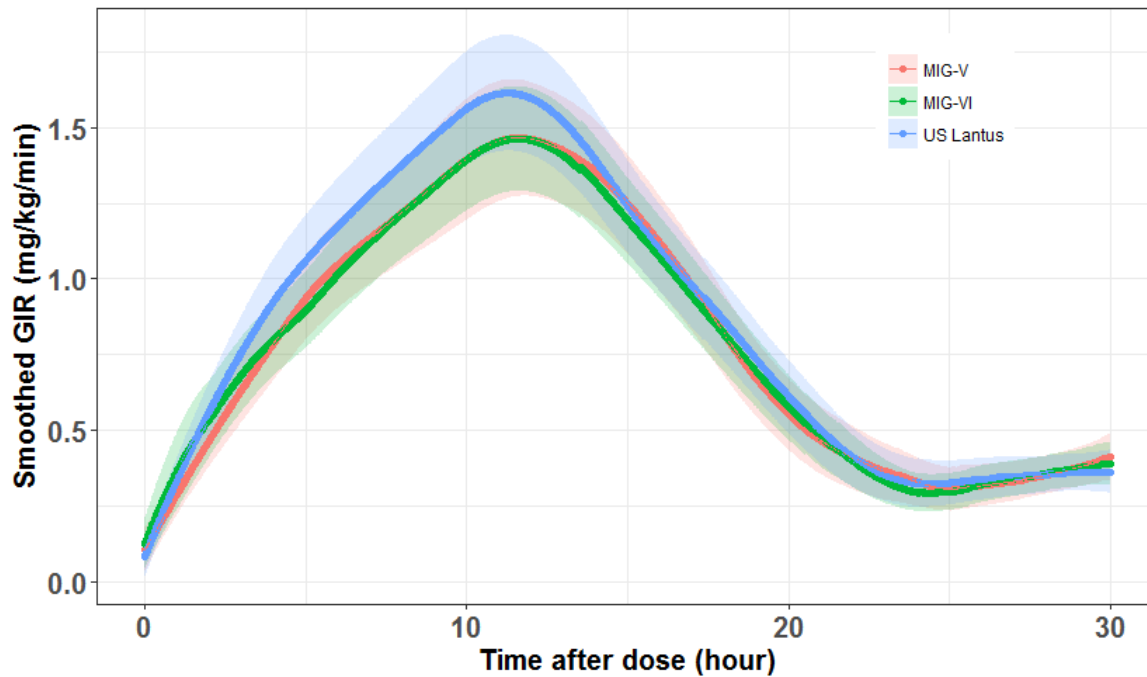
The duration of action was defined as time when blood glucose consistently above 150 mg/dL. Though Study MYL-1501D-1001 was a 30 hour euglycemic clamp study, many subjects have duration of action beyond 30 hours as indicated by the GIR-time and glucose-time profile (Figure 4- Figure 5).

Figure 3. Mean (90% CI) plasma insulin glargine concentration versus time profiles following single 0.5 unit/kg SC doses of MIG-V, MIG-VI and US-Lantus in Study MYL-1501D-1001. The LLOQ of 0.2 ng/mL was shown as a solid line.



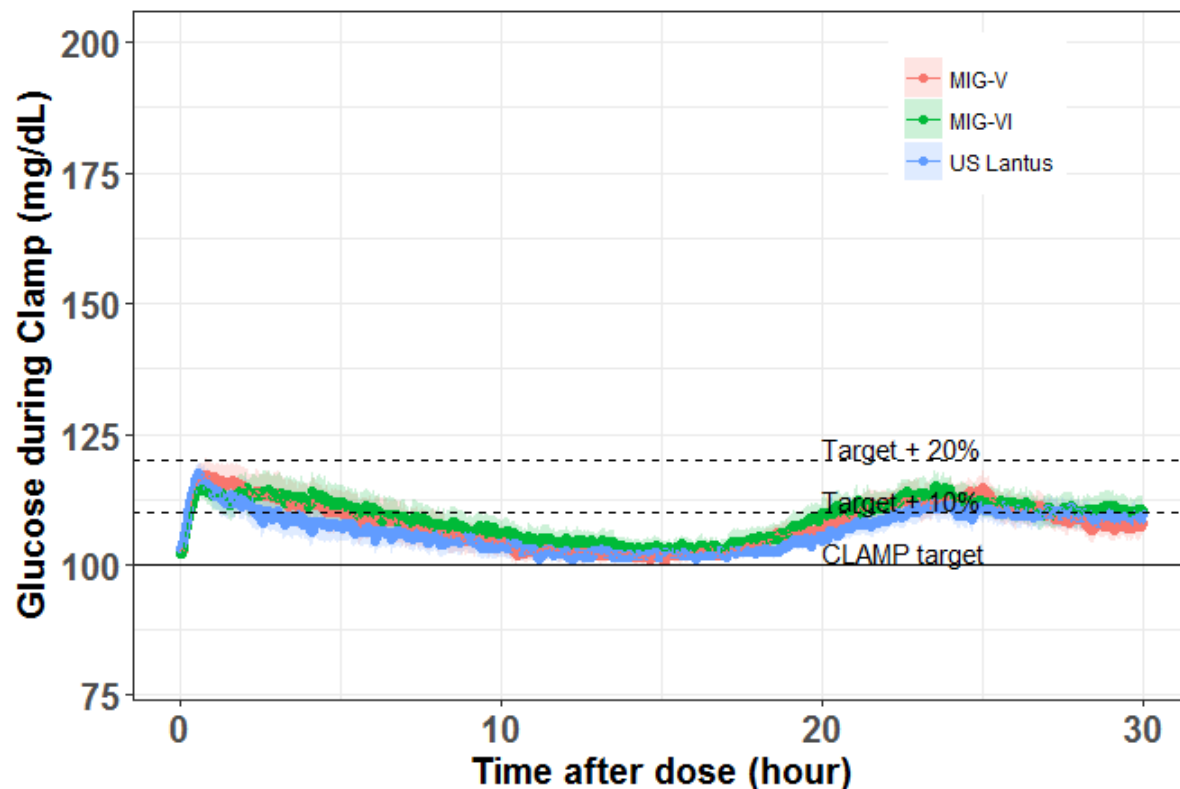
Source: Reviewer's analysis

Figure 4. Mean (90% CI) smoothed GIR versus time profiles following single 0.5 unit/kg SC doses of MIG-V, MIG-VI and US-Lantus in Study MYL-1501D-1001.



Source: Reviewer's analysis

Figure 5. Mean (90% CI) blood glucose concentration versus time profiles following single 0.5 unit/kg SC doses of MIG-V, MIG-VI and US-Lantus in Study MYL-1501D-1001.



Source: Reviewer's analysis

For the primary PK parameters (AUC_{0-24h} and C_{max} of insulin glargine metabolite M1), the equivalence criterion based on PK (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in all comparisons. Also for all secondary AUC parameters, the 90% CI of the ratio test/reference lay within these limits (Table 3 and Table 4).

For GIR_{max} , the 90% CIs of all three comparisons lay within the limits 80.00% and 125.00%. For $AUC_{GIR,0-24h}$, the 90% CIs of the comparisons between MIG-VI and US-Lantus, and between MIG-VI and MIG-V lay within the limits 80.00% and 125.00%, however, the lower side of the confidence interval when comparing MIG-V vs. US-Lantus fell slightly below on the lower side of the confidence interval, (78.30; 98.47) (Table 5 and Table 6).

While evaluating PD similarity using the secondary PD parameters, the geometric mean ratio (90% CI) showed significant difference for the following PD comparisons (Table 6):

- $AUC_{GIR,0-12h}$ ratio of 79.16% (66.81%; 93.80%), $AUC_{GIR,12-24h}$ ratio of 90.16% (79.50%; 102.25%), and $AUC_{GIR,0-last}$ ratio of 88.72% (79.51%; 99.0%) when compared MIG-V vs. US-Lantus
- $AUC_{GIR,0-12h}$ ratio of 85.74% (71.77%; 102.43%) when compared MIG-VI vs. US-Lantus

Table 3. Summary statistics of primary PK endpoint in Study MYL-1501D-1001.

Parameter [Unit]	Statistic	MIG-V	MIG-VI	US Lantus
AUC _{0-24h} [h*ng/mL]	N	103	101	102
	Mean	9.763	10.507	10.982
	SD	7.405	6.842	9.180
	CV%	75.846	65.122	83.592
	Min	4.000	4.307	4.165
	Median	8.436	8.972	9.123
	Max	73.538	57.090	88.085
	Geomean	8.674	9.375	9.670
GeoCV%	44.953	45.140	44.942	
C _{max} [ng/mL]	N	103	101	102
	Mean	0.575	0.636	0.638
	SD	0.455	0.418	0.516
	CV%	79.077	65.662	80.925
	Min	0.259	0.260	0.264
	Median	0.481	0.550	0.526
	Max	4.580	3.510	4.920
	Geomean	0.511	0.567	0.562
GeoCV%	43.693	45.359	45.530	

Source: Sponsor's analysis

Table 4. Treatment comparisons of PK parameters in Study MYL-1501D-1001

Parameter	Comparison	N	Ratio % ¹	90% CI ²	CV% ³
AUC _{0-24h}	MIG-V vs. US Lantus	98/98	92.82	(88.30; 97.56)	21.2
	MIG-VI vs. US Lantus	96/96	96.75	(91.49; 102.31)	23.6
	MIG-VI vs. MIG-V	97/97	105.08	(99.14; 111.37)	24.8
C _{max}	MIG-V vs. US Lantus	98/98	94.18	(89.55; 99.06)	21.5
	MIG-VI vs. US Lantus	96/96	100.60	(94.95; 106.58)	24.4
	MIG-VI vs. MIG-V	97/97	108.03	(101.69; 114.77)	25.8
AUC _{0-12h}	MIG-V vs. US Lantus	98/98	91.34	(86.25; 96.74)	24.6
	MIG-VI vs. US Lantus	96/96	94.45	(88.55; 100.74)	27.4
	MIG-VI vs. MIG-V	97/97	104.55	(97.59; 112.01)	29.5
AUC _{12-24h}	MIG-V vs. US Lantus	98/98	92.73	(86.84; 99.01)	28.2
	MIG-VI vs. US Lantus	96/96	98.59	(93.01; 104.50)	24.6
	MIG-VI vs. MIG-V	97/97	106.77	(99.16; 114.97)	31.8
AUC _{0-30h}	MIG-V vs. US Lantus	98/98	93.03	(88.44; 97.86)	21.6
	MIG-VI vs. US Lantus	96/96	96.24	(90.94; 101.84)	23.9
	MIG-VI vs. MIG-V	97/97	105.14	(99.43; 111.17)	23.7
AUC _{0-t}	MIG-V vs. US Lantus	98/98	93.22	(88.47; 98.22)	22.3
	MIG-VI vs. US Lantus	96/96	96.18	(90.69; 102.01)	24.9
	MIG-VI vs. MIG-V	97/97	105.10	(99.27; 111.29)	24.3
AUC _{0-∞}	MIG-V vs. US Lantus	63/67	94.24	(86.79; 102.33)	24.5
	MIG-VI vs. US Lantus	67/64	92.58	(84.83; 101.03)	25.4
	MIG-VI vs. MIG-V	67/63	104.10	(96.59; 112.21)	22.2

Analysis: ANOVA with log-transformed endpoint as response and clinical site, treatment, sequence, period, clinical site by sequence, and subject within (clinical site by sequence) as fixed effects.

¹ Geometric LS-mean ratio of treatments (test/reference), expressed in percent

² Two-sided 90% confidence interval

³ Intra-subject CV%

Source: Sponsor's analysis

Table 5. Summary statistics of primary PD endpoint in Study MYL-1501D-1001.

Parameter [Unit]	Statistic	MIG-V	MIG-VI	US Lantus
AUC _{GIR,0-24h} [mg/kg]	N	110	103	108
	Mean	1340.4	1423.2	1481.8
	SD	1140.9	969.68	1138.1
	CV%	85.1	68.1	76.8
	Min	60.94	65.87	106.63
	Median	998.20	1166.0	1191.8
	Max	6772.8	3827.5	6526.5
	Geomean	971.88	1059.0	1121.8
GeoCV%	101.6	105.0	95.5	
GIR _{max} [mg/kg/min]	N	110	103	108
	Mean	1.816	1.855	1.920
	SD	1.3315	1.0789	1.1876
	CV%	73.3	58.2	61.8
	Min	0.35	0.32	0.39
	Median	1.422	1.548	1.652
	Max	9.44	4.80	6.42
	Geomean	1.483	1.552	1.627
GeoCV%	69.5	68.9	63.5	

Source: Sponsor's analysis

Table 6. Treatment comparisons of PD parameters in Study MYL-1501D-1001

Parameter	Comparison	N	Ratio % ¹	90% CI ²	95% CI ²
AUC _{GIR,0-24h}	MIG-V vs. US Lantus	105/105	87.81	(78.30; 98.47)	(76.57; 100.69)
	MIG-VI vs. US Lantus	100/100	92.35	(80.25; 106.27)	(78.08; 109.22)
	MIG-VI vs. MIG-V	101/101	108.21	(95.58; 122.52)	(93.30; 125.52)
GIR _{max}	MIG-V vs. US Lantus	105/105	93.07	(85.55; 101.24)	(84.16; 102.91)
	MIG-VI vs. US Lantus	100/100	93.79	(84.59; 103.98)	(82.91; 106.10)
	MIG-VI vs. MIG-V	101/101	102.87	(94.05; 112.51)	(92.42; 114.49)
AUC _{GIR,0-12h}	MIG-V vs. US Lantus	104/105	79.16	(66.81; 93.80)	(64.63; 96.96)
	MIG-VI vs. US Lantus	100/100	85.74	(71.77; 102.43)	(69.32; 106.05)
	MIG-VI vs. MIG-V	101/101	113.39	(91.35; 140.75)	(87.58; 146.81)
AUC _{GIR,12-24h}	MIG-V vs. US Lantus	104/103	90.16	(79.50; 102.25)	(77.57; 104.79)
	MIG-VI vs. US Lantus	99/98	95.53	(82.35; 110.82)	(80.00; 114.07)
	MIG-VI vs. MIG-V	100/100	110.56	(96.67; 126.44)	(94.17; 129.79)
AUC _{GIR,0-last}	MIG-V vs. US Lantus	105/105	88.72	(79.51; 99.00)	(77.83; 101.14)
	MIG-VI vs. US Lantus	100/100	92.41	(80.29; 106.36)	(78.12; 109.32)
	MIG-VI vs. MIG-V	101/101	107.03	(94.72; 120.95)	(92.48; 123.87)

Analysis: ANOVA with log-transformed endpoint as response and clinical site, treatment, sequence, period, clinical site by sequence, and subject within (clinical site by sequence) as fixed effects.

¹ Geometric LS-mean ratio of treatments (test/reference), expressed in percent

² Two-sided 90% and 95% confidence intervals

Source: Sponsor's analysis

2.2.3 How are the results of PK and PD study of MYL-1501D related to the efficacy comparison of MYL-1501D versus US-Lantus?

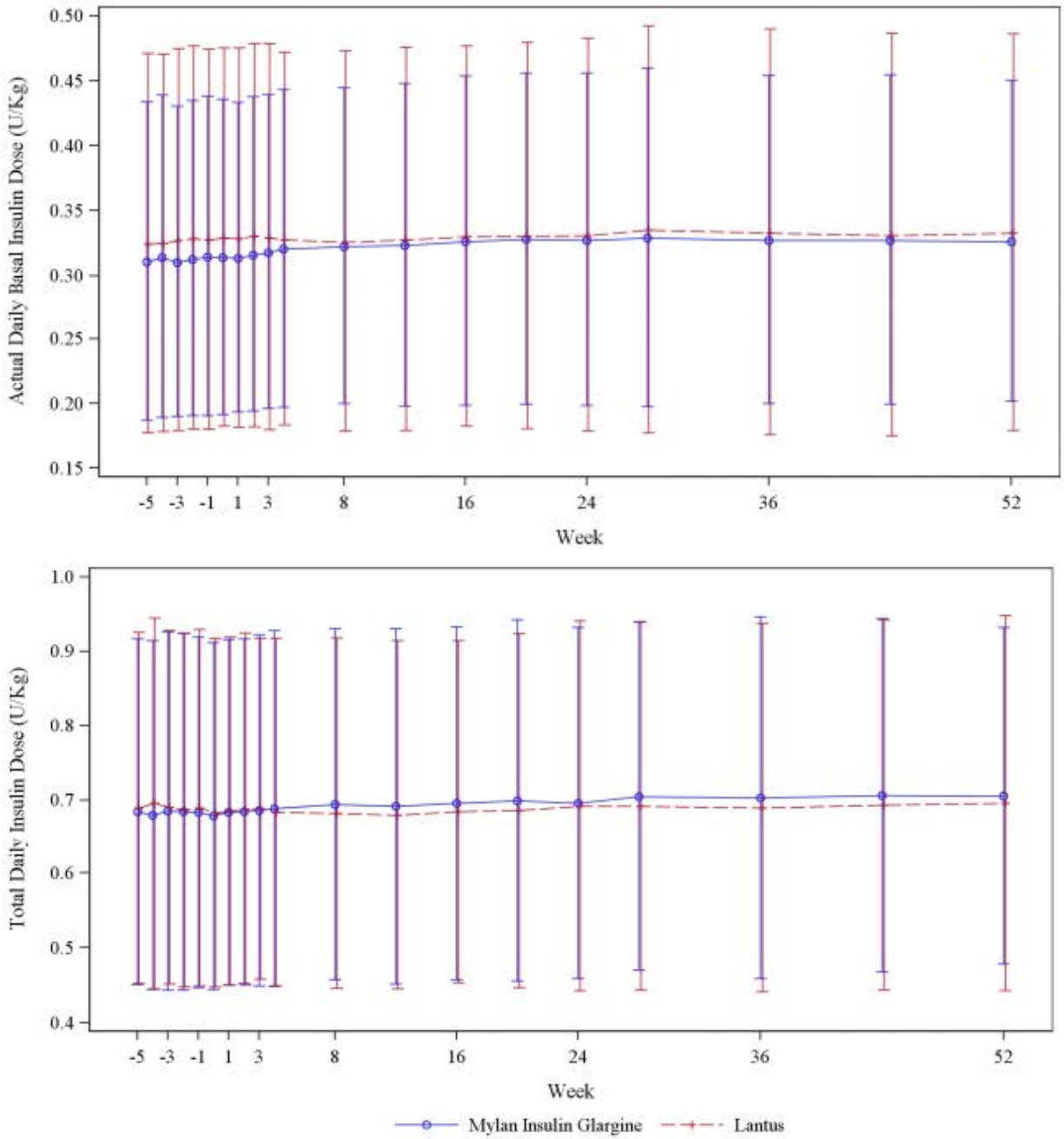
The sponsor conducted two randomized, open-label, active-controlled, parallel-group, non-inferiority Phase 3 trials in patients with type 1 diabetes (T1DM; MYL-GAI-3001) and type 2 diabetes (T2DM; MYL-GAI-3002) to assess the relative efficacy and safety of MYL-1501D compared to US-Lantus. As mentioned in section 2.1.2, MIG-V product was used in both Phase 3 trials, thus MYL-1501D refers to MIG-V product in this section and the safety results can't be extrapolated to MIG-VI, the to-be-marketed product. However, since MIG-VI is claimed to be the improvised version of MIG-V, the similarity in safety profile of MIG-V versus US-Lantus would otherwise inform about the clinical relevance of the factors for which, MIG-V was reportedly improvised, and relevance of such factors for MIG-VI (refer to CMC review for further details on evaluation of MIG-VI versus MIG-V products from a purity perspective).

The primary objective of these two Phase 3 studies was to test the hypothesis that MYL-1501D is non-inferior to US-Lantus according to the change in HbA1c from baseline to the 24-week endpoint when administered with mealtime insulin lispro. In these studies, patients in the control treatment group received US-Lantus (from Sanofi sourced from the US; 100 IU/mL) in all study sites. See Dr. Mitra Rauschecker's Clinical Review and Dr. Anna Kettermann's statistical review for detailed assessment of efficacy and safety of MYL-1501D in DARRTS.

The non-inferiority comparison in the clinical efficacy and safety studies assumes similar unit dose definition for the test and reference products, which is determined relying on the PK and PD similarity between MYL-1501D and US-Lantus.

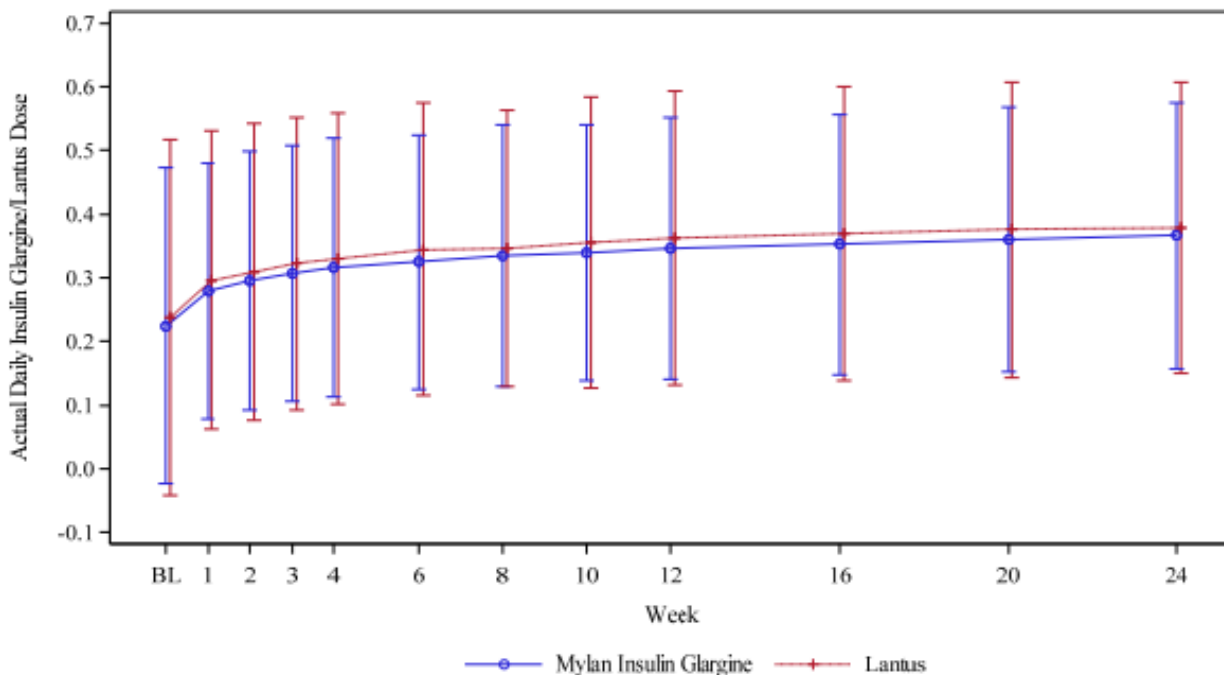
According to the overall dose-time profile for the basal and total insulins used in both clinical efficacy and safety studies, the trends of dose utilization were not different between MYL-1501D and US-Lantus (Figure 6 and 7).

Figure 6. Overall daily mean ($\pm$ SD) basal insulin dose (top panel), and total insulin dose (bottom panel) by treatment in patients with T1DM in study MYL-GAI-3001.



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

Figure 7. Overall daily mean ($\pm$ SD) basal insulin dose by treatment in patients with T2DM in study MYL-GAI-3002.



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

2.2.4 What are the design features and main findings of Study GLARGCT100111?

As mentioned in section 1.3, Study GLARGCT100111 was supportive, as this study didn't use the to-be-marketed product (MIG-VI). Thus, only summary using results from sponsor's analysis is provided here.

Study GLARGCT100111 was a phase 1, double-blind, randomized, single-center, single-dose, 3-way crossover euglycemic clamp study conducted in patients with T1DM at Profil Institut für Stoffwechselforschung GmbH, Germany. Single doses of 0.4 unit/kg of MIG-V, US-Lantus, and EU-Lantus were tested using the Biostator technic. The primary objective of the study was to compare the relative PK and PD properties of MIG-V 100 U/mL with Lantus 100 U/mL (US-Lantus and EU-Lantus) in patients with T1DM. The secondary objective was to assess single-dose safety and local tolerability of MIG-V 100 U/mL relative to the 2 reference products.

A total of 114 T1DM patients (90 males and 24 females) were included in the study and randomized to one of the six treatment sequences (19 subjects per sequence). One-hundred and twelve subjects completed all treatments according to the protocol. Two subjects withdrew consent after visit 2.

Table 7 displays the statistical analysis of the primary PK and PD parameters. The geometric mean test/reference ratios of the primary PK parameters ($AUC_{ins,0-30h}$ and $C_{ins,max}$) varied from 0.98 to 1.02 for each pairwise comparison. The corresponding 90% CIs for the pairwise

comparisons were well within the defined range of 0.8 to 1.25 for both parameters, indicating PK equivalence. Similarly, the ratios of the primary PD parameters ($AUC_{GIR,0-30h}$ and GIR_{max}) varied from 0.94 to 1.01. As expected, variability for the PD parameters was greater than that for the PK parameters; however, the 90% CIs for both primary PD parameters were within the range of 0.8 to 1.25 for each pairwise comparison, which indicated PD equivalence of the 3 treatments.

Table 7. Study GLARGCT100111 - Parametric Analysis of Primary PK and PD Parameters (sponsor's analysis)

Parameter	Products	N ^a	Geometric mean ratio (T/R)	90% CI
Primary PK parameters				
$AUC_{ins,0-30h}$ [pmol*h/L]	Lantus-EU vs. Lantus-US	51	1.01	0.95 - 1.07
	MYL-1501D vs. Lantus-EU	48	1.02	0.96 - 1.08
	MYL-1501D vs. Lantus-US	44	1.02	0.96 - 1.09
$C_{ins,max}$ [pmol/L]	Lantus-EU vs. Lantus-US	83	1.01	0.95 - 1.08
	MYL-1501D vs. Lantus-EU	84	0.98	0.92 - 1.05
	MYL-1501D vs. Lantus-US	78	1.00	0.93 - 1.06
Primary PD parameters				
$AUC_{GIR,0-30h}$ [mg/kg]	L (EU) vs. L (US)	104	0.97	0.85 - 1.11
	MYL-1501D vs. L (EU)	104	0.97	0.85 - 1.11
	MYL-1501D vs. L (US)	103	0.94	0.82 - 1.07
GIR_{max} [mg/kg/min]	L (EU) vs. L (US)	102	0.98	0.90 - 1.07
	MYL-1501D vs. L (EU)	103	1.01	0.92 - 1.10
	MYL-1501D vs. L (US)	102	0.99	0.91 - 1.08

a: N is the number of patients analyzed after elimination of individual profiles according to the rules defined in [Section 9.8.2 of GLARGCT100111CSR](#). Dosing periods of subjects with no PD response or only very low PD response were excluded from the per protocol population for PD. A subject was considered to have a very low PD response if the $AUC_{GIR,0-24h}$ was less than 50 mg/dL

Source: Table 2 and 4 of Summary of Clinical Pharmacology Studies

The sponsor also performed post hoc analysis includes all profiles. All PK profiles were included and insulin glargine concentrations were calculated using the assay subtraction method. The results were shown in table 8:

Table 8. Study GLARGCT100111 - Post Hoc Analyses of Primary PK Parameters using all profiles (sponsor's analysis)

Parameter	Pairwise comparison	Geometric mean ratio (T/R)	90% CI
<i>Analysis 1: Inclusion of all profiles</i>			
AUC _{ins, 0-30h}	Lantus-EU vs. Lantus-US	1.02	0.95 - 1.09
	MYL-1501D vs. Lantus-EU	0.95	0.89 - 1.02
	MYL-1501D vs. Lantus-US	0.97	0.90 - 1.04
C _{ins,max}	Lantus-EU vs. Lantus-US	1.00	0.93 - 1.08
	MYL-1501D vs. Lantus-EU	1.02	0.95 - 1.10
	MYL-1501D vs. Lantus-US	1.02	0.95 - 1.10

Source: Table 3 of Summary of Clinical Pharmacology Studies

The above analysis with all limitations of post-hoc analysis, serves as a sensitivity analysis substantiating the results of primary analysis. Though it reflects due attention paid by the applicant to analytical challenges faced in the study. The PD analysis, which included all subjects and demonstrated similarity between MIG-V and US-Lantus and lack of PD difference between US-Lantus and EU-Lantus, reduces the residual uncertainties originating from PK data.

2.3 Bioanalytical

2.3.1 Is the bioanalytical method properly validated to measure MYL-1501D and Lantus?

The sponsor used a validated liquid chromatography-tandem mass-spectrometry (LC-MS/MS) bioanalytical assay to measure plasma parent glargine, M1, and M2 metabolite concentrations (b) (4) report 8286484). Briefly, the sponsor treated the plasma samples using solid phase extraction. Stable isotopic labelled insulin glargine, M1, and M2 metabolite were used as the internal standard. The volume is 300 µL per sample. The sponsor used a linear calibration regression with a weighting factor of 1/x to quantitate all analytes. The lower limit of quantification of the assay is 0.2 ng/mL. See Table 7 for the summary of assay validation such as within-run and between-run precision and accuracy for all analytes.

Overall, the bioanalytical assay for measuring MYL-1501D and Lantus are acceptable with reasonable accuracy and precision.

2.3.2 Was an Office of Study Integrity and Surveillance (OSIS) inspection requested for the clinical study?

The Division of Metabolism and Endocrinology Products requested an OSIS inspection for the clinical and bioanalytical sites of MYL-1501D-1001 through Michael G White dated September 14, 2017 (Reference ID: 4152688 in DARRTS).

The Division of New Drug Bioequivalence Evaluation within OSIS recommended accepting the bioanalytical data from Study MYL-1501D-1001 (NDA 210605). The final inspection classification is No Action Indicated (NAI) for the clinical sites. See memorandum by Dr. Li-Hong Yeh dated Feb 28, 2018 (Reference ID: 4227991 in DARRTS). For the bioanalytical site, the outcome of the inspections at (b) (4) was classified as Voluntary Action Indicated (VAI). See memorandum by Dr. Gajendiran Mahadevan dated March 22, 2018

(Reference ID: 4238325 in DARRTS). For Study GLARGCT100111, the clinical and bioanalytical sites are the same as that of Study MYL-1501D-1001.

Table 9. Summary of assay validation for MYL-1501D and Lantus bioanalytical assay for Study MYL-1501D-1001.

Analytes	Glargine Glargine M1 Glargine M2
Species	Human
Analytical matrix	K ₂ EDTA plasma
Internal standard (ISTD)	Glargine: Glargine SIL Glargine M1: Glargine M1 SIL Glargine M2: Glargine M2 SIL
Validated method	HB-13-017
Validated range	Glargine: 0.2 to 5 ng/mL Glargine M1: 0.2 to 5 ng/mL Glargine M2: 0.2 to 5 ng/mL
Quality control (QC) levels	Glargine: 0.2 ng/mL, 0.6 ng/mL, 1.5 ng/mL, 4 ng/mL, 20 ng/mL Glargine M1: 0.2 ng/mL, 0.6 ng/mL, 1.5 ng/mL, 4 ng/mL, 20 ng/mL Glargine M2: 0.2 ng/mL, 0.6 ng/mL, 1.5 ng/mL, 4 ng/mL, 20 ng/mL
Analytical technique/method of detection	Solid phase extraction/liquid chromatography with tandem mass spectrometric detection
Sample volume	300 µL
Calibration model	Glargine: Linear Glargine M1: Linear Glargine M2: Linear
Weighting factor	Glargine: 1/x Glargine M1: 1/x Glargine M2: 1/x
Precision and accuracy	Requirements fulfilled

Stability of standard stock solutions	Glargine: 6 hours on wet ice Glargine: 9 days at nominal -80°C Glargine SIL: 6 hours on wet ice Glargine M1: 6 hours on wet ice Glargine M1: 14 days at nominal -80°C Glargine M1 SIL: 6 hours on wet ice Glargine M2: 6 hours on wet ice Glargine M2: 14 days at nominal -80°C Glargine M2 SIL: 6 hours on wet ice
Processed-sample stability	179 hours refrigerated
Haemolysis assessment	Acceptable (Glargine – additional peak observed in LoQC samples, haemolysed samples to be annotated for Glargine in sample study)
Hyperlipidaemic plasma assessment	Acceptable
Selectivity in disease state matrix (type 1 diabetes mellitus)	Acceptable
Co-administered drug, Actrapid (human insulin) at 2.5 ng/mL	Acceptable
Sample collection stability	Glargine: two hours at room temperature Glargine: two hours on wet ice Glargine M1: two hours at room temperature Glargine M1: two hours on wet ice Glargine M2: two hours at room temperature Glargine M2: two hours on wet ice
Freeze-thaw matrix stability	Glargine: 4 cycles at nominal -20°C and nominal -80°C Glargine M1: 4 cycles at nominal -20°C and nominal -80°C Glargine M2: 4 cycles at nominal -20°C and nominal -80°C
Room temperature and wet ice matrix stability	Glargine: 18 hours Glargine M1: 18 hours Glargine M2: 18 hours
Long-term frozen matrix stability	Glargine: 137 days at nominal -20°C Glargine: 137 days at nominal -80°C Glargine M1: 137 days at nominal -20°C Glargine M1: 137 days at nominal -80°C Glargine M2: 137 days at nominal -20°C Glargine M2: 137 days at nominal -80°C
Maximum validated analytical run	96 injections

Source: (b) (4) report 8286484

3 Preliminary Labeling Recommendations

Labeling comments will be captured in a separate addendum as needed.

4 Appendix: Synopsis of Study MYL-1501D-1001

Name of Sponsor/Company: Mylan GmbH		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Insulin glargine, MIG-V and MIG-VI		
Title of Trial: A glucose clamp trial investigating the biosimilarity of two formulations of Mylan's insulin glargine with US Lantus® reference product* * Original clinical documents erroneously classified the objective of the study to assess biosimilarity of two formulations. Although this was the formal name of the trial protocol, more accurately the trial investigated the bioequivalence of two preparations of Mylan's insulin glargine produced using different manufacturing processes as compared with US Lantus.		
Coordinating Investigator: Oliver Klein, Profil Institut für Stoffwechselforschung GmbH, Neuss Principal Investigator: PD Dr. med. Leona Plum-Mörschel, Profil Mainz GmbH & Co. KG		
Trial Centers: 1) Profil Institut für Stoffwechselforschung GmbH, Hellersbergstr. 9, 41460 Neuss, Germany 2) Profil Mainz GmbH & Co. KG, Malakoff Passage, Rheinstr. 4c, 55116 Mainz, Germany		
Publication (Reference): None at the time of writing this report		
Trial Period: 29 November 2016 until 04 March 2017	Phase of Development: 1	
Objectives: <u>Primary objective:</u> The primary objective was to demonstrate bioequivalence with regard to the total exposure, based on the M1 metabolite of insulin glargine, during one dosing interval (AUC_{0-24h}) of two preparations of Mylan's insulin glargine (MIG) 100 U/mL (derived from two different manufacturing processes) with Lantus® 100 U/mL (US reference listed drug (RLD)) in subjects with Type 1 diabetes. Bioequivalence between test and reference product was demonstrated if the 90% confidence interval (CI) of the ratio test/reference for M1 AUC_{0-24h} was contained in the acceptance interval of 0.8-1.25 (80.00%–125.00%). <u>Secondary objectives:</u> The secondary objectives were to compare additional pharmacokinetic (PK) and pharmacodynamic (PD) properties and to assess the single dose safety and tolerability of two preparations of Mylan's insulin glargine (MIG) 100 U/mL and of Lantus® 100 U/mL (US RLD).		
Methodology / Trial Design: The trial was a Phase I, two-center, randomized, double-blind, 3-treatment, 3-period crossover trial comparing single doses of MIG-V (i.e., drug product from process V) and MIG-VI insulin glargine (i.e., drug product from process VI) with US RLD Lantus. Each subject participated in 6 visits: an informed consent visit (at least one day before Visit 1), a		

screening visit (Visit 1, 1 to 28 days before Visit 2) to check eligibility for participation, three dosing visits (Visits 2, 3 and 4, separated by a washout period of 5 to 21 days), and a follow-up visit with final examination (Visit 6, 1 to 10 days after Visit 4). At Visits 2, 3 and 4, the three insulin products were administered in 6 randomly allocated sequences in the setting of a 30-hour computer-controlled euglycemic glucose clamp (ClampArt). During the clamp procedure blood was collected pre-dose until 30 hours' post-dose in pre-specified intervals for measurement of blood glucose (BG) and insulin glargine metabolite 1 (M1).

Number of Subjects (planned and analyzed):

One hundred and fourteen (114) male subjects with Type 1 diabetes were planned to be included in the trial in order to ensure that 100 subjects completed the trial. Actually, 116 subjects were randomized and 113 were completers.

Diagnosis and Main Criteria for Inclusion:

Male subjects with Type 1 diabetes, with age between 18 and 64 years (both inclusive), body mass index (BMI) between 18.5 and 29.0 kg/m² (both inclusive), HbA1c ≤9.0% and fasting negative C-peptide (≤0.30 nmol/L) were eligible to participate in this trial. Subjects were required to be on a stable insulin regimen for at least 2 months prior to screening, with a total daily insulin dose of less than 1.2 (I)U/kg. Apart from their diabetes, they had otherwise to be generally healthy. Subjects were excluded from the trial if one of the exclusion criteria, as pre-defined in the trial protocol, was met. Informed consent was to be obtained before any trial-related activities.

Test Product, Dose and Mode of Administration, Batch Number:

1. Mylan's MIG-V insulin glargine, 100 U/mL in 3 mL cartridges. Manufacturer: Biocon Limited, India, batch no.: BS15005852 (provided using packing batch-no. BM16001834), expiry date: 10/2017. Single dose of 0.5 U/kg body weight, administered subcutaneously (s.c.) at Visits 2, 3, or 4.
2. Mylan's MIG-VI insulin glargine, 100 U/mL, in 3 mL cartridges. Manufacturer: Biocon sdn, Malaysia, batch no.: BS15009376, expiry date: 03/2018. Single dose of 0.5 U/kg body weight, administered s.c. at Visits 2, 3, or 4.

Duration of Treatment:

The planned trial duration per subject was 4 weeks. The treatment consisted of 3 single dose administrations, two of test and one of reference product, separated by 5 to 21 days between dosing visits.

Reference Therapy, Dose and Mode of Administration, Batch Number:

US RLD Lantus[®] (insulin glargine, 100 U/mL), in disposable 3 mL pens (SoloStar[®]). Manufacturer: Sanofi, batch no.: 6F3682A, expiry date: 04/2019. Single dose of 0.5 U/kg body weight, administered s.c. at Visits 2, 3, or 4.

Criteria for Evaluation:

PK endpoints:

- Primary endpoint: AUC_{0-24h}, area under the M1 concentration curve from 0 to 24 hours

Secondary PK endpoints:

- C_{max}, maximum observed M1 concentration
- AUC_{0-12h}, AUC_{12-24h}, AUC_{0-30h}, areas under the M1 concentration curve in the indicated time intervals
- AUC_{0-t}, derived as the AUC from dosing to the time point of the last quantifiable measurement (C_{last}) (above lower limit of quantification (LLOQ))
- AUC_{0-∞}, defined as AUC_{0-t} + C_{last}/λ_z
- t_{max}, time to maximum observed M1 concentration
- t_{1/2}, terminal elimination half-life calculated as ln(2)/λ_z

- λ_z , terminal elimination rate constant

PD endpoints (all secondary):

- $AUC_{GIR,0-24h}$, $AUC_{GIR,0-12h}$, $AUC_{GIR,12-24h}$, areas under the glucose infusion rate curve in the indicated time-intervals
- $AUC_{GIR,0-last}$, area under the glucose infusion rate curve from 0 hours until the end of clamp
- GIR_{max} , maximum observed glucose infusion rate
- $t_{max,GIR}$, time to maximum glucose infusion rate
- Duration of action, time until BG level is consistently above 150 mg/dL

Safety endpoints:

Adverse events (AEs), including hypoglycemic episodes and injection site reactions, clinical laboratory safety variables, physical examination, vital signs, and electrocardiograms (ECGs)

Statistical Methods:

All statistical analyses were performed using SAS[®] (SAS Institute Inc., Cary, North Carolina, USA), Version 9.3 (PK analyses) and 9.4 (remaining analyses).

The statistical analysis of the primary PK endpoint employed a general linear model analysis (proc-GLM) of variance (ANOVA) using clinical site, treatment, sequence, period, clinical site by sequence, and subject within (clinical site by sequence) as fixed effects. Within the model, least square mean (LS-mean) for each treatment as well as the difference of the means between the treatment groups and corresponding 90% confidence intervals (CIs) were calculated and back-transformed (exponentially transformed) in order to find the estimated ratio of responses between the insulin preparations, and the corresponding 90% CIs. If the 90% CIs of the ratios of responses for AUC_{0-24h} fell within the conventional limits of the acceptance interval (80.00%; 125.00%), PK equivalence could be demonstrated. Three separate ANOVA models were conducted – one for each comparison excluding the data from the treatment that was not relevant for the comparison.

The secondary PK endpoints C_{max} , AUC_{0-12h} , AUC_{12-24h} , AUC_{0-30h} , AUC_{0-t} and $AUC_{0-\infty}$, were compared for the three insulin products using the same statistical approach as for the primary PK endpoint. These endpoints, however, were not required to meet the equivalence criteria.

The PD endpoints, $AUC_{GIR,0-24h}$, $AUC_{GIR,0-12h}$, $AUC_{GIR,12-24h}$, $AUC_{GIR,0-last}$, and GIR_{max} , were analyzed using logarithmic-transformed data, and the same linear model ANOVA was used as for PK parameters. Within the model, the LS-mean for each treatment as well as the difference of the means between the treatment groups and corresponding 90% and 95% CIs were calculated and back-transformed (exponentially transformed) in order to find the estimated ratios of responses between the insulin preparations, and the corresponding CIs. Three separate ANOVA models were conducted – one for each comparison excluding the data from the treatment that was not relevant for the comparison.

The PK endpoints t_{max} , $t_{1/2}$ and λ_z , the PD endpoints $t_{max,GIR}$ and duration of action, and the safety endpoints were analyzed using summary statistics by treatment only.

Data analysis for PK and PD was based on the per-protocol population (PPP), which included all subjects of the full analysis set (FAS, comprising all randomized subjects) who had completed the trial without any important protocol violations. Drop-outs or subjects with evaluable data for only one treatment were excluded from the PPP. Furthermore, dosing periods of subjects with less than 8 measurements above LLOQ and/or baseline concentrations > 5% of C_{max} were excluded from the PPP for PK, and dosing periods of subjects with lack of or only very low PD response (i.e. $AUC_{GIR,0-24h}$ < 50 mg/kg) were excluded from the PPP for PD. The safety analysis set included all subjects receiving at least one dose of IMP.

A sensitivity analysis was performed on the above PK endpoints using all concentration-time profiles with at least one quantifiable concentration but excluding those with pre-dose concentrations > 5% of C_{max} and Period 2 for Subject no. (b) (6)

A second sensitivity analysis was performed on the above PD endpoints utilizing the FAS, except drop-

outs, periods where $AUC_{GIR,0-24h}$ was zero, and Period 2 for Subject no. (b) (6). Furthermore, a post-hoc analysis based on arithmetic instead of geometric LS-means (according to Fieller's theorem) was performed on the above PD endpoints in order to account for subjects with a very low or zero PD response. This analysis was based on the FAS, except drop-outs and Period 2 for Subject no. (b) (6).

SUMMARY – CONCLUSIONS

One hundred and sixteen (116) male subjects with Type I diabetes were randomized to one of 6 treatment sequences. One (1) subject discontinued after randomization but before intake of investigational medical product (IMP). Thus, 115 subjects with age from 18 to 63 years (mean = 41.3 years), a BMI from 19.6 to 29.0 kg/m² (mean = 25.64 kg/m²), a HbA1c from 4.9 to 9.0% (mean = 7.33%), and fasting C-peptide not higher than 0.28 nmol/L (mean = 0.045 nmol/L) received at least one dose of IMP. Three (3) subjects discontinued after randomization so that 113 subjects were trial completers. The PPP comprised 112 (all trial completers, except subject no. (b) (6) with 2 non-evaluable PK profiles, who therefore was also excluded from PD analysis) and the safety analysis set 115 subjects ((i.e., all subjects who received at least a single dose).

Pharmacokinetics and Pharmacodynamics:

PK Results

The following two tables display the summary statistics of the PK endpoints and the results of the statistical comparisons (PPP for PK).

Parameter [Unit]	N	MIG-V	N	MIG-VI	N	US Lantus
AUC_{0-24h} [h*ng/mL]	103	9.763 (7.405) ¹	101	10.507 (6.842) ¹	102	10.982 (9.180) ¹
C_{max} [ng/mL]	103	0.575 (0.455) ¹	101	0.636 (0.418) ¹	102	0.638 (0.516) ¹
AUC_{0-12h} [h*ng/mL]	103	4.660 (3.319) ¹	101	4.941 (2.963) ¹	102	5.308 (4.353) ¹
AUC_{12-24h} [h*ng/mL]	103	5.103 (4.188) ¹	101	5.566 (4.031) ¹	102	5.674 (4.919) ¹
AUC_{0-30h} [h*ng/mL]	103	11.343 (9.019) ¹	101	12.223 (8.414) ¹	102	12.797 (10.951) ¹
AUC_{0-t} [h*ng/mL]	103	11.222 (9.052) ¹	101	12.089 (8.462) ¹	102	12.667 (10.987) ¹
$AUC_{0-\infty}$ [h*ng/mL]	66	17.174 (8.971) ¹	70	19.577 (14.255) ¹	68	19.371 (10.650) ¹
t_{max} [h]	103	12.00 (3.00 - 22.00) ²	101	12.00 (3.00 - 20.00) ²	102	12.00 (2.00 - 30.00) ²
$t_{1/2}$ [h]	66	14.73 (9.09) ¹	70	16.45 (10.75) ¹	68	17.53 (23.78) ¹
λ_z [1/h]	66	0.0589 (0.0261) ¹	70	0.0585 (0.0315) ¹	68	0.0589 (0.0327) ¹

¹ Arithmetic mean (Standard deviation)

² Median (Range)

Parameter	Comparison	N	Ratio % ¹	90% CI ²	CV% ³
AUC_{0-24h}	MIG-V vs. US Lantus	98/98	92.82	(88.30; 97.56)	21.2
	MIG-VI vs. US Lantus	96/96	96.75	(91.49; 102.31)	23.6
	MIG-VI vs. MIG-V	97/97	105.08	(99.14; 111.37)	24.8
C_{max}	MIG-V vs. US Lantus	98/98	94.18	(89.55; 99.06)	21.5
	MIG-VI vs. US Lantus	96/96	100.60	(94.95; 106.58)	24.4
	MIG-VI vs. MIG-V	97/97	108.03	(101.69; 114.77)	25.8
AUC_{0-12h}	MIG-V vs. US Lantus	98/98	91.34	(86.25; 96.74)	24.6
	MIG-VI vs. US Lantus	96/96	94.45	(88.55; 100.74)	27.4
	MIG-VI vs. MIG-V	97/97	104.55	(97.59; 112.01)	29.5
AUC_{12-24h}	MIG-V vs. US Lantus	98/98	92.73	(86.84; 99.01)	28.2
	MIG-VI vs. US Lantus	96/96	98.59	(93.01; 104.50)	24.6
	MIG-VI vs. MIG-V	97/97	106.77	(99.16; 114.97)	31.8

AUC _{0-30h}	MIG-V vs. US Lantus	98/98	93.03	(88.44; 97.86)	21.6
	MIG-VI vs. US Lantus	96/96	96.24	(90.94; 101.84)	23.9
	MIG-VI vs. MIG-V	97/97	105.14	(99.43; 111.17)	23.7
AUC _{0-t}	MIG-V vs. US Lantus	98/98	93.22	(88.47; 98.22)	22.3
	MIG-VI vs. US Lantus	96/96	96.18	(90.69; 102.01)	24.9
	MIG-VI vs. MIG-V	97/97	105.10	(99.27; 111.29)	24.3
AUC _{0-∞}	MIG-V vs. US Lantus	63/67	94.24	(86.79; 102.33)	24.5
	MIG-VI vs. US Lantus	67/64	92.58	(84.83; 101.03)	25.4
	MIG-VI vs. MIG-V	67/63	104.10	(96.59; 112.21)	22.2

Analysis: ANOVA with log-transformed endpoint as response and clinical site, treatment, sequence, period, clinical site by sequence, and subject within (clinical site by sequence) as fixed effects.

¹ Geometric LS-mean ratio of treatments (test/reference), expressed in percent

² Two-sided 90% confidence interval

³ Intra-subject CV%

For the primary endpoint (AUC_{0-24h} of insulin glargine metabolite M1), the equivalence criterion based on PK (90% CI of the ratio test/reference within the limits 80.00% and 125.00%) was met in all comparisons. Also for all secondary AUC-endpoints and for C_{max} the 90% CI of the ratio test/reference lay within these limits.

PD Results

The following tables display the summary statistics of the (secondary) PD endpoints and the results of the statistical comparisons (PPP for PD).

Parameter [Unit]	N	MIG-V	N	MIG-VI	N	US Lantus
AUC _{GIR,0-24h} [mg/kg]	110	1340.4 (1140.9) ¹	103	1423.2 (969.68) ¹	108	1481.8 (1138.1) ¹
GIR _{max} [mg/kg/min]	110	1.816 (1.3315) ¹	103	1.855 (1.0789) ¹	108	1.920 (1.1876) ¹
AUC _{GIR,0-12h} [mg/kg]	110	704.91 (611.80) ¹	103	756.81 (541.84) ¹	108	815.08 (625.74) ¹
AUC _{GIR,12-24h} [mg/kg]	110	635.54 (592.64) ¹	103	666.43 (500.89) ¹	108	666.75 (558.85) ¹
AUC _{GIR,0-last} [mg/kg]	110	1461.7 (1230.1) ¹	103	1550.8 (1040.1) ¹	108	1608.6 (1208.5) ¹
t _{max,GIR} [h]	110	11.725 (0.00 - 30.00) ²	103	11.300 (0.00 - 20.45) ²	108	11.133 (0.00 - 30.00) ²
Duration of action [h]	110	30.00 (20.60 - 30.00) ²	103	30.00 (19.03 - 30.00) ²	108	30.00 (17.38 - 30.00) ²

¹ Arithmetic mean (Standard deviation)

² Median (Range)

Parameter	Comparison	N	Ratio % ¹	90% CI ²	95% CI ²
AUC _{GIR,0-24h}	MIG-V vs. US Lantus	105/105	87.81	(78.30; 98.47)	(76.57; 100.69)
	MIG-VI vs. US Lantus	100/100	92.35	(80.25; 106.27)	(78.08; 109.22)
	MIG-VI vs. MIG-V	101/101	108.21	(95.58; 122.52)	(93.30; 125.52)
GIR _{max}	MIG-V vs. US Lantus	105/105	93.07	(85.55; 101.24)	(84.16; 102.91)
	MIG-VI vs. US Lantus	100/100	93.79	(84.59; 103.98)	(82.91; 106.10)
	MIG-VI vs. MIG-V	101/101	102.87	(94.05; 112.51)	(92.42; 114.49)
AUC _{GIR,0-12h}	MIG-V vs. US Lantus	104/105	79.16	(66.81; 93.80)	(64.63; 96.96)
	MIG-VI vs. US Lantus	100/100	85.74	(71.77; 102.43)	(69.32; 106.05)
	MIG-VI vs. MIG-V	101/101	113.39	(91.35; 140.75)	(87.58; 146.81)
AUC _{GIR,12-24h}	MIG-V vs. US Lantus	104/103	90.16	(79.50; 102.25)	(77.57; 104.79)
	MIG-VI vs. US Lantus	99/98	95.53	(82.35; 110.82)	(80.00; 114.07)
	MIG-VI vs. MIG-V	100/100	110.56	(96.67; 126.44)	(94.17; 129.79)

AUC _{GIR,0-last}	MIG-V vs. US Lantus	105/105	88.72	(79.51; 99.00)	(77.83; 101.14)
	MIG-VI vs. US Lantus	100/100	92.41	(80.29; 106.36)	(78.12; 109.32)
	MIG-VI vs. MIG-V	101/101	107.03	(94.72; 120.95)	(92.48; 123.87)

Analysis: ANOVA with log-transformed endpoint as response and clinical site, treatment, sequence, period, clinical site by sequence, and subject within (clinical site by sequence) as fixed effects.

¹ Geometric LS-mean ratio of treatments (test/reference), expressed in percent

² Two-sided 90% and 95% confidence intervals

For GIR_{max} both 90% and 95% CIs of all three comparisons lay within the limits 80.00% and 125.00%. The point estimates of the other comparisons supported PD equivalence. However, the trial was not powered for PD equivalence and therefore, it is not surprising that the CIs were not within the standard equivalence margins. These data excluded subjects with an AUC_{GIR,0-24h} <50 mg/kg, which was pre-specified in the protocol.

Given that some subjects had very low PD response, which is not unusual, an additional analysis was performed that included all data irrespective of the clamp value. However, for this analysis, geometric mean was not an optimal methodology for assessment. Therefore, the arithmetic mean using Fieller's theorem was used and the analysis is shown in the following table.

Parameter	Comparison	N	Ratio % ¹	90% CI ²	95% CI ²
AUC _{GIR,0-24h}	MIG-V vs. US Lantus	113/113	91.87	(82.34; 102.12)	(80.51; 104.27)
	MIG-VI vs. US Lantus	112/112	92.46	(81.97; 104.52)	(80.04; 107.13)
	MIG-VI vs. MIG-V	112/112	101.14	(90.10; 114.22)	(88.10; 117.12)
GIR _{max}	MIG-V vs. US Lantus	113/113	96.05	(87.08; 105.52)	(85.36; 107.46)
	MIG-VI vs. US Lantus	112/112	93.26	(83.92; 103.65)	(82.18; 105.84)
	MIG-VI vs. MIG-V	112/112	97.35	(87.76; 108.43)	(86.01; 110.84)
AUC _{GIR,0-12h}	MIG-V vs. US Lantus	113/113	87.58	(77.99; 97.86)	(76.15; 100.01)
	MIG-VI vs. US Lantus	112/112	89.14	(78.01; 101.85)	(75.96; 104.60)
	MIG-VI vs. MIG-V	112/112	102.16	(89.21; 117.56)	(86.87; 120.99)
AUC _{GIR,12-24h}	MIG-V vs. US Lantus	113/113	97.06	(86.28; 108.77)	(84.21; 111.25)
	MIG-VI vs. US Lantus	112/112	96.56	(85.43; 109.48)	(83.39; 112.32)
	MIG-VI vs. MIG-V	112/112	100.01	(89.16; 113.05)	(87.19; 116.00)
AUC _{GIR,0-last}	MIG-V vs. US Lantus	113/113	92.32	(83.18; 102.05)	(81.42; 104.07)
	MIG-VI vs. US Lantus	112/112	92.88	(82.83; 104.33)	(80.97; 106.81)
	MIG-VI vs. MIG-V	112/112	101.24	(90.65; 113.74)	(88.73; 116.52)

Analysis: ANOVA with untransformed endpoint as response and clinical site, treatment, sequence, period, clinical site by sequence as fixed effects, and subject within (clinical site by sequence) as random effect.

¹ Arithmetic LS-mean ratio of treatments (test/reference), expressed in percent

² Two-sided 90% and 95% confidence intervals

In this analysis based on arithmetic means, the 90% and 95% CIs for GIR_{max} and AUC_{GIR,0-24h} lay within the 80.00% and 125.00% limits. The only comparison that was outside the confidence limit was for AUC_{GIR,0-12h} (MIG-V and MIG-VI vs. US Lantus). However, this isolated deviation was not unusual because this trial was not designed to demonstrate equivalence in PD parameters.

Safety Results:

Sixteen (16) subjects (14.2%) experienced at least one treatment-emergent AE (TEAE) after administration of MIG-V, 14 subjects (12.2%) after administration of MIG-VI, and 20 subjects (17.7%) after US Lantus. The respective numbers of single events were 23, 21 and 29, yielding a total number of 73 TEAEs.

No serious AEs or deaths occurred, and none of the AEs resulted in a subject's withdrawal from the trial. All TEAEs were of mild (18 events in 12 subjects after MIG-V, 14 events in 11 subjects after MIG-VI, 22 events in 15 subjects after US Lantus) or moderate (5 events in 5 subjects after MIG-V, 7 events in 5 subjects after MIG-VI, 7 events in 7 subjects after US Lantus) intensity; no TEAE was rated as being of severe intensity. Except for one TEAE (increased creatine phosphokinase after MIG-VI, with outcome recovering/resolving), all TEAEs had the outcome recovered/resolved.

The most frequent TEAE was hypoglycemia, with 12 events (in 7 subjects, 6.2%) following MIG-V, 9 events (in 7 subjects, 6.1%) following MIG-VI, and 10 events (in 7 subjects, 6.2%) following US Lantus administration. All cases of hypoglycemia were rated as mild. Two (2) cases of hypoglycemia (1 after MIG-VI and 1 after US Lantus) were assessed as being possibly related to IMP administration.

The second most frequent TEAE was headache, with 3 events (in 3 subjects, 2.7%) following MIG-V, 3 events (in 3 subjects, 2.6%) following MIG-VI, and 8 events (in 8 subjects, 7.1%) following US Lantus administration. Seven (7) cases of headache (1 after MIG-V and 6 after US Lantus) were rated as mild and 7 (2 after MIG-V, 3 after MIG-VI, 2 after US Lantus) as moderate. Three (3) headaches (one after each treatment) were assessed as being possibly related to IMP administration.

There were 7 TEAEs which were assessed as related to IMP administration: Two (2) cases of mild hypoglycemia (one after MIG-VI and another after US Lantus), one case of mild nausea after US Lantus, a moderate increase in creatine phosphokinase after MIG VI, and 3 cases of mild/moderate headache (each one after MIG-V, MIG-VI, and US Lantus, respectively).

Besides the increase in creatine phosphokinase, there were no further clinically significant findings or changes in laboratory test results. There were no clinically significant findings or changes in vital signs, ECGs, and physical examination results.

CONCLUSIONS**Pharmacokinetic and Pharmacodynamic Conclusions:**

- Based on the primary PK endpoint, AUC_{0-24h} of the insulin glargine metabolite M1, both MIG-V and MIG-VI were bioequivalent to US Lantus[®], and MIG-VI was bioequivalent to MIG-V, since the 90% CIs of the respective geometric mean ratios test/reference lay within the acceptance interval of 80.00% to 125.00%.
- All secondary PK endpoints (AUC_{0-12h} , AUC_{12-24h} , AUC_{0-30h} , AUC_{0-t} , $AUC_{0-\infty}$ and C_{max}) supported PK equivalence for all three pairwise comparisons.
- In the PD analysis using geometric mean, and excluding all treatments with zero or very low PD response (i.e. $AUC_{GIR,0-24h}$ below 50 mg/kg), supported the PK equivalence with a few measurements outside the 80.00%–125.00% range.
- The analysis based on arithmetic means (according to Fieller's theorem), that included all clamp values, supported the PK equivalence for almost all three pairwise comparisons (i.e., the 90% CIs of the respective arithmetic mean ratios test/reference lay within 80.00% and 125.00% interval).

Safety Conclusions:

- Both MIG-V and MIG-VI preparations, as well as US Lantus[®], were safe and well tolerated at a single s.c. dose of 0.5 U/kg, when administered to male subjects with Type 1 diabetes mellitus.
- With regard to their safety profiles, all treatments were comparable.

Date of Report: 21 April 2017 (Final Version 1.0)

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

/s/

JING NIU
04/24/2018

MANOJ KHURANA
04/24/2018