STATISTICAL ANALYSIS PLAN

MYL-1501D-3003

AN OPEN-LABEL, RANDOMIZED, MULTI-CENTER, PARALLEL-GROUP CLINICAL TRIAL COMPARING THE EFFICACY AND SAFETY OF MYLAN'S INSULIN GLARGINE WITH LANTUS® IN TYPE 1 DIABETES MELLITUS PATIENTS: AN EXTENSION STUDY

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V1.0 (Dated 27JUL2016) for Protocol MYL-1501D-3003 Version V2.0, dated 06-MAY 2016.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Final V1.0	27JUL2016	Neetu Badhoniya and Yogesh Sonawane	Not Applicable – First Version

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	American Diabetes Association
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
ALT	Alanine Transaminase
ANCOVA	Analysis Of Covariance
AST	Aspartate Transaminase
BMI	Body Mass Index
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
DCCT	Diabetes Control And Complications Trial
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End Of Treatment
FDA	Food and Drug Administration (United States)
FPG	Fasting Plasma Glucose
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCP	Host Cell Protein
HIV	Human Immunodeficiency Virus
ITT	Intention To Treat
IU	International Unit
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDL	Low Density Lipoprotein
LS	LSmeans
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
mITT	Modified Intent-To-Treat
NAb	Neutralizing Antibody
PP	Per Protocol
SAE(s)	Serious Adverse Event(s)
SD	Standard Deviation

SMBG	Self-Monitored Blood Glucose
TEAE	Treatment Emergent Adverse Event
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol MYL-1501D-3003. It describes the data to be summarized and analyzed, including the specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version V2.0, dated 06-MAY-2016.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to test whether Mylan's insulin glargine once daily treatment sequence is equivalent to Lantus® once daily treatment sequence (based on change in [glycosylated hemoglobin] HbA1C from baseline at week 36 when administered in combination with mealtime insulin lispro.

2.2. SECONDARY OBJECTIVES

To compare treatment sequence group of Mylan's insulin glargine to Lantus®, at 36 weeks, when administered in combination with mealtime insulin lispro with respect to:

1. Change in basal insulin dose per unit body weight (U/Kg/day).
2. Immunogenicity: incidence and change from baseline in the relative levels of ADA, incidence and change from baseline in the relative levels of anti-HCP antibodies.
3. Rate of hypoglycemic events per 30 days; and occurrence of hypoglycemia
4. Occurrence of local reactions, systemic reactions and other adverse events.
5. Change in fasting plasma glucose from baseline.
6. Change in 8-point (self-monitored blood glucose) SMBG profile from baseline
7. Device related safety assessment.

3. STUDY DESIGN

Patients with an established diagnosis of T1DM per ADA 2014 criteria who were randomized to the Lantus® treatment arm of the MYL-GAI-3001 study, and who have completed the 52-week treatment period on Lantus® will be eligible to be screened for the study MYL-1501D-3003. The purpose of this study is to assess the interchangeability through testing equivalence between two treatment sequences with respect to the primary end point, Mylan's insulin glargine and Lantus®. Eligible patients from MYL-GAI-3001 study who successfully completed 52 weeks on

Lantus® will be randomized 1:1 to one of the treatment sequences. Treatment sequence arm 1 - Mylan's insulin glargine for 12 weeks in period 1 then switched to Lantus® for next 12 weeks in period 2 and additional switch to Mylan's insulin glargine for additional 12 weeks to complete the third treatment period. Treatment sequence arm 2 - Lantus® for 12 weeks in period 1, continue to receive Lantus® in period 2 for 12 weeks and in period 3 for another 12 weeks.

Twelve weeks exposure in each period is considered adequate to assess the efficacy with respect to HbA1c, as well as to compare the safety between the treatment sequence groups. If switching from Lantus® to Mylan's insulin glargine or from Mylan's insulin glargine to Lantus® have an impact on the efficacy or the safety, a discernible difference in efficacy or safety parameters is expected versus the group of patients who are continuing on Lantus® throughout.

After 36 weeks of treatment, patients will resume their baseline treatment with prescribed medications and will have a safety follow up visit after 4 weeks resulting in a total study duration of 40 weeks.

3.1. GENERAL DESCRIPTION

Study Duration:

The maximum possible duration of patient participation in the extension trial is 40 weeks, which includes:

- Treatment period 1: 12 weeks (Week 0 to Week 12).
- Treatment period 2: 12 weeks (Week 12 to Week 24).
- Treatment period 3: 12 weeks (Week 24 to Week 36).
- Follow-up period: 4 weeks follow-up visit (Week 36 to Week 40)

Number of Patients:

Approximately 138 patients with type 1 diabetes who completed the 3001 study on the Lantus will participate in this trial. Approximately 69 patients will be randomized to one of two sequence groups (Treatment sequence arm 1: Mylan's insulin glargine switch to Lantus® sequence group and switch back to Mylan's insulin glargine, or Treatment sequence arm 2: Lantus® to Lantus® to Lantus® sequence group) in a 1:1 ratio. No replacement of patients will be performed if a patient discontinued prematurely from the study. For the modified intent-to-treat (mITT) population, power to demonstrate equivalence with ±0.4% limits will be 90% with 10% patients who don't have at least one baseline and one last period HbA1c data. The power is calculated assuming no true mean group difference and a 0.61% standard deviation. This standard deviation is based on published results for clinical studies with Lantus®.

Allocation to Treatment

Patients who completed the 3001 study on Lantus® will be randomized 1:1 to receive either Mylan's insulin glargine or Lantus® using an IVRS/IWRS. Change of dosing from morning to bedtime or vice versa will not be permitted. If a patient discontinues, the patient will not be allowed to re-enter the extension study.

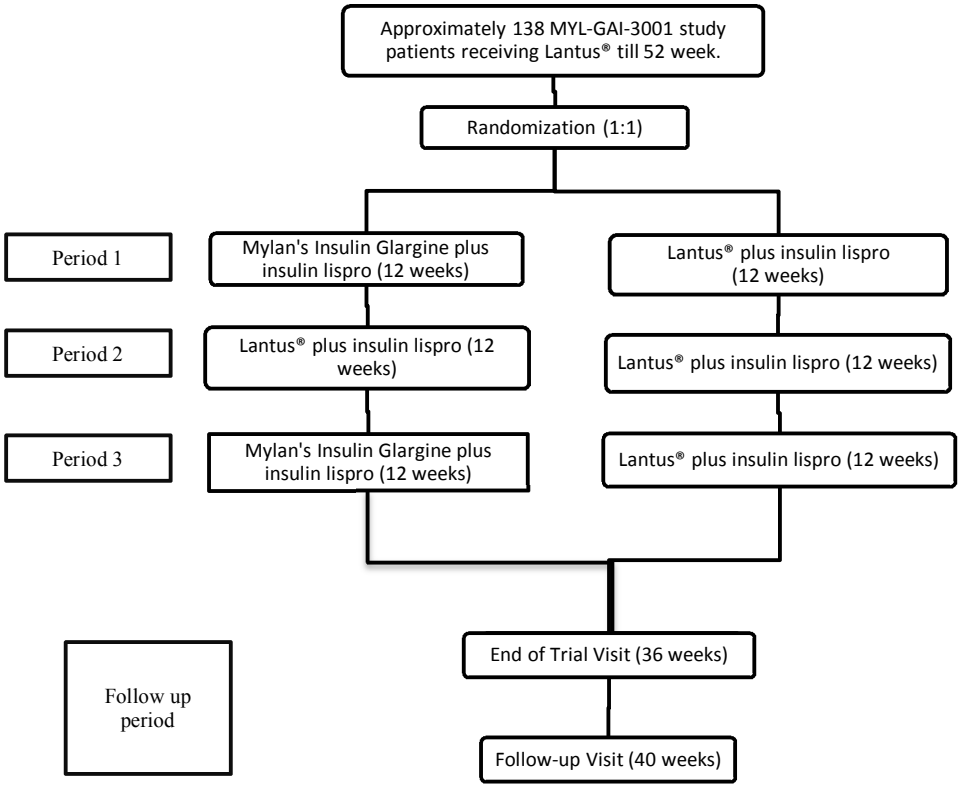
Blinding

This is an open-label study. To minimize bias, treatment assignments will not be revealed to the central laboratory for the safety (immunogenicity) and efficacy (HbA1c) analyses.

Study Treatment

The investigational products used in this trial are Mylan's insulin glargine (test product) and Lantus® from Sanofi-Aventis (reference product). All patients will receive insulin lispro as mealtime medication.
Both investigational products will be provided in a pre-filled disposable pen with a 3 mL cartridge. Mylan's insulin glargine formulation for injection is a, sterile, clear solution at pH 4. Each mL contains 100 units of insulin glargine (equivalent to 3.64 mg). The excipients of the formulation are identical to those of Lantus®.
Humalog (insulin lispro injection, 100 IU/mL), is manufactured by Eli Lilly (administered in Humalog disposable pens).

Table A: Study Flow Chart



3.2. SCHEDULE OF EVENTS

Schedule of events can be found in protocol synopsis (pages 18-19) of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

- An error was found for primary endpoint in Section 9.2.1 Wording “at 12 week” was deleted.
- The results with MMRM ANCOVA from secondary efficacy analysis will also be used to compare primary analysis results as robustness check. Other sensitivity analyses are added in Section 15.1.4 by using multiple imputation method.

3.4. NOT APPLICABLE SIGNIFICANT CHANGES FROM PREVIOUS AUTHORIZED VERSION

Not Applicable

4. PLANNED ANALYSES

The following analyses will be performed for this study:

Final Analysis

4.1. INTERIM ANALYSIS

Not Applicable.

4.2. FINAL ANALYSIS

All planned analyses identified in this SAP will be performed by Quintiles Biostatistics team following sponsor authorization of this SAP and Database Lock.

5. ANALYSIS SETS

Agreement and authorization of patient included/ excluded from each analysis set will be conducted prior to the final database lock of the study.

All analysis sets described below will be derived at final analysis, based on available data.

5.1. RANDOMIZED POPULATION [RND]

The Randomized (RND) population will contain all patients who are enrolled and randomized to study medication.

For analyses and displays based on RND, patients will be classified according to randomized treatment sequence group.

5.2. SAFETY POPULATION

The safety population includes patients who are randomized and take at least one dose of the trial drug. Safety population will be mainly used for safety analyses.

If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis.

5.3. INTENT-TO-TREAT POPULATION [ITT]

The ITT population includes all randomized patients (including patients who receive incorrect treatment sequence, do not complete the trial or do not comply with the protocol or used prohibited medication) and have baseline (week 0 visit) and at least one post-baseline visit. The patients under ITT population will be analyzed according to the planned treatment sequence. ITT population will be used for secondary variable analyses.

The sensitivity analysis to check the robustness of primary analysis will be based on the ITT population. All secondary efficacy analyses will be based on the ITT population.

5.4. MODIFIED INTENT-TO-TREAT POPULATION [MITT]

The mITT population includes all randomized patients (including patients who receive incorrect treatment sequence, do not complete the trial or do not comply with the protocol or used prohibited medication) and have at least one baseline (week 0 visit) HbA1c value and one post-baseline HbA1c value at treatment period 3 (24 < Week ≤ 36). The mITT will be used for primary analysis.

5.5. PER PROTOCOL POPULATION [PP]

The PP population includes patients who have at least one baseline and one period 3 value and do not have protocol violations that impact the primary outcome. The patients excluded from the PP population will be identified before database lock (i.e., before unblinding the study team). All protocol deviations and the deviations impacting the primary outcome variable will be documented separately and will be signed off prior to the database lock (i.e., before unblinding the study team). PP population will be used for sensitivity analysis for primary variable.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of first dose of study medication (Day 1 is the day of the first dose of study medication in extension study), and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is visit 1, which includes the post study measurements from week 52 of the main study MYL-GAI-3001 and assessment prior to receiving randomized treatment sequence group (including unscheduled assessments) in extension study. In the case where the last non-missing measurement and the randomized treatment sequence group start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the randomized treatment sequence group start date will be considered post-baseline.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the best/ worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries.

Early termination data will be mapped to the next available visit number for by-visit summaries.

Listings will include scheduled, unscheduled, retest, and early discontinuation data.

6.4. WINDOWING CONVENTIONS

Allowed time window for each visit will performed as mentioned in protocol **Schedule of Activities** (page numbers 18 and 19).

6.5. STATISTICAL TESTS

All tests of treatment effects will be conducted at a two-sided alpha level of 0.05 or with 2-sided 95% confidence intervals, unless otherwise specified.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as: Test Value at Visit X – Baseline Value

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.2 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Geographical Region (Categories North America/ Europe)
- Baseline value (Continuous Variable)

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers globally. Randomization to treatment sequence arms is stratified by region.

Geographical region will be categorized as follows:

Geographic Region	Country
North America	United States of America, Canada

Europe	Latvia, Estonia, Slovakia, Czech Republic, Hungry, Germany

A term for treatment by region interaction will not be included in the primary analysis model, however, a sensitivity analysis, based on the primary model but including a term for treatment sequence by region interaction, will be performed.

7.3. MISSING DATA

Missing primary and secondary efficacy and safety analysis data will be not imputed except when week 36 HbA1c data is missing due to early discontinuation, exit measurement of that period will be used for endpoint. In addition, for sensitivity analysis of multiple imputation method, if missing values occur in more than 10% of the patients for HbA1C values, then monotone regression for multiple imputations will be used.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustment for multiplicity will be performed.

7.5. ACTIVE-CONTROL STUDY INTENDED TO SHOW EQUIVALENCE

For primary endpoint analysis, equivalence for efficacy will be supported if the two sided 95% confidence interval for the difference of mean change from baseline between two sequence groups for HbA1c is within ±0.4%.
Two-sided 95% CI will be derived using ANCOVA model which includes region, treatment sequence as fixed effects, and baseline HbA1c as a covariate.

7.6. EXAMINATION OF SUBGROUPS

No subgroup analysis is planned.

8. OUTPUT PRESENTATIONS

For safety and efficacy presentations, the order and naming of the treatment sequence group will be as follows.

- MYL-IG Seq (to Mylan's insulin glargine to Lantus® to Mylan's insulin glargine)
- Lantus® Seq (to Lantus® to Lantus® to Lantus® sequence group)

All descriptive safety and efficacy summaries will be presented by treatment sequence group and be broken down by visit for each period.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

The frequency and percentage of randomized patients who completed the trial or discontinue early will be summarized for each treatment sequence group. The comparison of patient discontinuations across treatment sequence groups will be performed using the Fisher's exact test. Reason for discontinuation from the study will also be summarized.

The number and proportion of patients withdrawing from the study during screening will be presented in a table. Additionally, the number and proportion of patients in each population will be summarized.

A listing of patients who did not meet the inclusion/exclusion criteria will be produced.

A list of significant protocol violations will be provided. A summary of significant protocol violations will also be provided as frequency and percentages, and treatment sequence group comparisons will be performed using the Fisher's exact test. Refer Appendix 2 for significant protocol violation.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the randomized population.

Patient characteristics will be recorded prior to randomization or already collected in the MYL-GAI-3001 trial and will be listed and summarized by treatment sequence group. Overall summaries will include descriptive statistics for continuous measures (n, mean, standard deviation, median, minimum and maximum) and for categorical measures (n, frequency, and percent).

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of randomization
- Gender
- Race
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m2)
- Duration of diabetes (years)
- Basal insulin timings (Morning/Evening)
- Baseline fasting plasma blood glucose
- Baseline HbA1c
- Fasting C-peptide, HIV, HBsAg, and HCVAb
- Region

10.1. DERIVATIONS

- BMI (kg/ m2) = weight (kg)/ height (m)2
- Duration of diabetes (years) = (Date of screening – date of onset of diabetes+1) /365.25

10.2. STATISTICAL TESTS FOR BASELINE CHARACTERISTICS

Treatment sequence groups will be compared by using t-tests for quantitative measures and the Fisher's exact test or the chi-squared test for categorical measures to investigate if there are any significant differences in baseline characteristics. The p-value for the corresponding two-sided test will be presented.

11. MEDICAL HISTORY

Medical History information will be presented for the safety population, and coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 18.1.

Medical history will be recorded at screening and will include pre-existing diseases or conditions reported at time of screening, which are resolved/stopped stop prior randomization, other than the study condition.

Frequency and percentage of Medical History conditions will be presented by treatment sequence groups and preferred term.

12. MEDICATIONS

Medications will be presented for the safety population and coded using WHO Drug dictionary 1DEC2015.

Prior and concomitant medications at enrollment will be summarized using ATC level 3 coding.

- 'Prior' medications are medications which started and stopped prior to the first dose of randomized study medication.
- 'Concomitant' medications are medications which:
  - started prior to, on or after the first dose of randomized study medication,
  - AND ended after the dose of randomized study medication or were ongoing at the end of the study.

See Appendix 1 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

Percentage of patients with at least 10% and overall concomitant medications will be summarized for each treatment period by treatment sequence groups as counts and percentages.

12.1. STATISTICAL TEST FOR CONCOMITANT MEDICATION

Treatment sequence groups for percentages of patients with at least 10% and overall concomitant medications will be compared using Chi-square test. P-value for the corresponding two-sided test will be presented.

13. STUDY MEDICATION EXPOSURE

Total treatment duration (in days) will be summarized for each treatment sequence and by period. The sequence group will be compared using t-test. Descriptive statistics for continuous measures will be presented along with the p-value for treatment sequence comparison.

Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

13.1. DERIVATIONS

Total treatment duration = date of last intake of study medication prior to the scheduled visit (Week 36) – date of first intake of study medication + 1.

It will be presented in days.

14. STUDY TREATMENT NON-COMPLIANCE

Patient will be identified as study treatment non-compliant if the patient meets any following criteria:

- Missing either total meal time insulin or basal insulin doses for 5 consecutive days.
- Missing either total meal time insulin or basal insulin doses for more than 30 accumulative days for completer or more than 20% treatment days for drop-out.
- Taking more than one administration of basal insulin (If multiple injections are required to deliver the required quantity of drug due to logistic reasons, then it is considered as one administration) for 10 days cumulative.
- Taking more than the prescribed basal insulin dose for more than 30 days cumulative.

Number and proportion of patients with noncompliance will summarized along with individual reasons for non-compliance.

15. EFFICACY OUTCOMES

Summaries will include descriptive statistics for continuous measures (n, mean, standard deviation, median, minimum and maximum) and for categorical measures (n, frequency, and percent).

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy outcome is change in HbA1c from baseline at week 36. .

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

The imputation will not be applied. If week 36 HbA1c is missing then last non-missing values from period 3 will be used.

15.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary objective of this study is to test the equivalence of changes in HbA1C between two treatment sequence groups at week 36.

The primary efficacy analysis will be performed for the mITT population.

ANCOVA will be performed on the primary outcome variable and the model will include region and sequence group as fixed effect and baseline value (52 weeks in MYL-GAI-3001) as covariate using mITT population. A 95% confidence interval for the difference between two treatment sequence groups for mean change from baseline HbA1c at endpoint will be produced using the ANCOVA method. Equivalence of Mylan's insulin glargine sequence group to Lantus® sequence group will be established if the 95% confidence interval is within ±0.4% equivalence limits.

The Least Square (LS) means for each treatment sequence group and associated standard errors will be derived. Differences in LS means will be calculated and associated 2-sided 95% confidence intervals will be provided.

15.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

A further robustness check will be conducted using the PP population and applying the same ANCOVA procedure as described in Section 15.1.3. Any differences in the conclusion will be further investigated by examining differences between the mITT and the PP populations.

Additional sensitivity analysis will be performed based on MMRM ANCOVA from secondary efficacy analysis. A repeated measures analysis employing a restricted maximum likelihood (REML)-based, mixed-effects model approach (MMRM) will be used to produce a 95% confidence interval for the difference between Mylan's insulin glargine sequence and Lantus® sequence for mean change of HbA1c at week 36. The MMRM model will include the fixed, categorical effect of treatment sequence group, region, visit, treatment sequence-by-visit interaction and baseline value (52 weeks in MYL-GAI-3001) as covariates.

A further robustness check will be done using the PP population and applying the same MMRM procedure as described in Section 15.1.3 to establish equivalence. Any differences in conclusions will be further investigated by examining differences in the ITT and the PP populations.

Other sensitivity analysis addressing missing data be conducted as following

Multiple imputed datasets will be generated based on the assumption of a monotone missing data pattern. The imputation will be performed using the monotone regression method for week 24 and week 36 sequentially. The variables treatment region, previous exposure to insulin and basal insulin dosing time will be used as independent variables.

An example of the SAS code using monotone regression for multiple imputation for week 36 (visit 13).

```
PROC MI DATA=XXX OUT=OXXX NIMPUTE=100 SEED=1122015;
    VAR Baseline VISIT13 VISIT9 VISIT5 ARMCD PSTRTRGN;
    CLASS ARMCD PSTRTRGN;
    MONOTONE REG (VISIT5 = BASELINE ARMCD PSTRTRGN);
    MONOTONE REG (VISIT9 = BASELINE VISIT5 ARMCD PSTRTRGN);
    MONOTONE REG (VISIT13 = BASELINE VISIT9 VISIT5 ARMCD PSTRTRGN);
RUN;
```

Imputation for the week 36 will be performed using the set with values imputed. In case non-monotone missing data (usually relatively infrequent) will be imputed using the Markov Chain Monte Carlo (MCMC) option prior to the above regression approach.

All imputed datasets will be analyzed using the same model parameters as used in the additional sensitivity analysis, and the results will be combined using Rubin's rules

An example of the SAS code for combining results using Rubin's rules with PROC MIANALYZE is given below:

```
ODS OUTPUT PARAMETERESTIMATES=MIESTDIFF ;
    PROC MIANALYZE DATA=LSDIFF;
      MODELEFFECTS LSMEANSDIFF;
       STDERR STDERR;
    RUN;
```

This approach will be performed for the ITT and the PP populations.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the ITT population.

A repeated measures analysis employing a restricted maximum likelihood (REML)-based, mixed-effects model approach (MMRM) will be used to compare treatment sequence diffference at scheduled visits. The MMRM model will include the fixed, categorical effect of treatment sequence group, region, visit, treatment sequence-by-visit interaction and baseline value (52 weeks in MYL-GAI-3001) as covariates. The data collected at Baseline, all schedule visits will be used in the MMRM model for the purpose of analysis. For the drop-out patients, if the last post baseline data is not falling at the scheduled visit, then it will be mapped to the next scheduled visit and this data will also be included in the analysis.

An unstructured covariance matrix will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If the model for unstructured covariance matrix fails to converge, the heterogeneous Toeplits covariance structure, followed by heterogeneous auto regressive covariance structure, will be used. If a structured covariance matrix is used because of the convergence

problem, an analysis will be conducted where a sandwich estimator will be used for the fixed effects parameters to take account of possible misspecification of the true covariance matrix.

Above mentioned statistical analysis approach will be performed for all secondary continuous efficacy variables. Contrasts of LS mean at each scheduled visit will be used to evaluate all pairwise treatment sequence group comparisons, and 95% confidence intervals for treatment sequence group differences in LS means will be computed for each visit.

Following efficacy measures (both actual and change values) will be summarized at baseline (week 52 in MYL-GAI-3001) and scheduled visits.

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

Change from baseline calculation will be done as defined in Section 6.6.

15.2.1.1. HbA1c

The measurement will be performed by the central laboratory for efficacy and safety samples.

15.2.1.2. Fasting plasma glucose

The measurement of fasting plasma glucose will be performed by the central laboratory for efficacy and safety samples. 'Fasting' is defined as no intake of food or drink (except water) for at least 10 hours.

15.2.1.3. Change in 8-point SMBG profile from baseline

8-point SMBG profile measurements will be performed by the patient at home and recorded in the patient diary, A single 8-point SMBG profile set includes measurements of SMBG values on 3 days, performed in the week preceding the next visit (of the three days, 2 should be consecutive). The patient should document the 3 pre-visit measurements in the diary, and will be advised to similarly document any additional estimations.

Individual pre-meal, individual post-meal, individual 2-hour excursion after meal, bedtime, overall (average) pre-meal, overall post-meal, overall excursion, 4-point average (pre-meal + bedtime), and daily average at scheduled visits will be computed.

For overall mean of blood glucose (BG), values for the SMBG profiles will be averaged over the specific time points in a day. Then this averaged value per day will be averaged across three days. The missing values will not be imputed. The daily average SMBG will not be computed for a day if the SMBG measurement was missing for more than 3 time points on a particular day. The SMBG overall average will be kept missing if the daily average is missing for all three days. If SMBG average is missing for one or two days, the SMBG average of the remaining days will be considered for the computation.

The average SMBG value across the three days at a particular visit and time point will be considered for the SMBG values at specific time points. For individual pre-meal, the average of pre-breakfast, pre-lunch and pre-dinner measurements within a day will be considered. The individual pre-meal values will be averaged across three days for overall average of pre-meal values. The individual post meal and overall post meal values will be computed in the same manner.

SMBG individual excursion values will be obtained by subtracting post-meal values with pre-meal values, it will be

applicable for morning excursion, noon excursion and evening excursion on the respective days. For overall excursion at morning, afternoon and evening, the individual excursion values obtained on each day will be averaged across three days.

For 4-point average, pre-meal and bedtime SMBG measurements will be averaged for a particular day and then this average value will be averaged across three days.

15.2.1.4. Daily insulin dose/unit body weight (daily prandial injectable, basal insulin and total) for days of 8-point profiles

Patients will be asked to document the dose of Mylan's insulin glargine/Lantus® and insulin lispro taken on the days when they perform 8-point SMBG profiles (from week 0 to week 36). Doses will be recorded in the patient diary. This data will be transcribed to the eCRF after the patient diary is collected, by the investigator or designee at scheduled visits. The patient should document the 3 pre-visit estimations in the diary; and will be advised to document any additional estimations.

There will be three dose variables – daily prandial insulin, basal insulin dose and total insulin dose.

Daily prandial insulin dose (meal time insulin dose) per day is the sum of all the daily prandial insulin dose for a day and then averages for number of days measured.

Basal insulin dose is the average of the insulin glargine or insulin Lantus dose over days measured. If the basal insulin dose is missing for a particular day of collection, total insulin dose will not be computed for that day. The total insulin dose will be computed for the remaining days were basal insulin dose is collected. The total insulin dose available at the remaining days will be used for the computation of average total insulin dose. For the computation of total daily prandial doses, the patients with at least three daily prandial doses at a particular day are considered. Total daily prandial dose will not be computed for a day if the daily prandial dose is recorded less than 3 times in a day and the total daily prandial dose computed at the remaining days will be used for the computation of average total daily prandial dose across the days.

Total insulin is the sum of daily prandial and basal insulin and then averaged for days measured. The missing insulin doses will not be considered for the average computation. All dose will be divided by total body weight (kg) to convert to daily insulin dose (U)/unit body weight (kg).

15.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLES

Not applicable.

15.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

15.2.3.1. Analysis of change from baseline in HbA1c

Descriptive statistics for HbA1c will be presented by treatment sequence group for actual and change from baseline (week 52 result from MYL-GAI-3001) to scheduled visits.

Treatment sequence group comparison will be done using the MMRM model, including treatment sequence, visit, treatment sequence-by-visit interaction, region as fixed effects, and baseline values as covariates.

LS means for each treatment sequence group and associated standard errors will be derived. Differences in LS means will be calculated and associated 2-sided 95% confidence intervals (p-value, as required) will be provided. These will be derived from the calculation of Type III sum-of –square and LS means from MMRM model.

For graphical display at each visit, LS means and 95% CI will be generated from the MMRM model including treatment sequence group, visit, treatment- sequence group by-visit interaction, region as fixed effects, and baseline values as covariates. In addition, mean (± SD) plot will be prepared for actual HbA1c measurements by visit.

15.2.3.2. Analysis of change from baseline in fasting plasma glucose

Descriptive statistics will be presented by treatment sequence group for actual and change from baseline (week 52 result from MYL-GAI-3001) to scheduled visits for fasting plasma glucose.

Treatment sequence group comparison will be done using the MMRM model, including treatment sequence group, visit, treatment sequence group-by-visit interaction, region, as fixed effects, and baseline values as covariates.

LS means for each treatment sequence group and associated standard errors will be derived. Differences in LS means will be calculated and associated 2-sided 95% confidence intervals (p-value, as required) will be provided. These will be derived from the calculation of Type III sum-of –square and LS means from MMRM model.

15.2.3.3. Analysis of Change in 8-point SMBG profile from baseline

8-point SMBG profile at a visit will be calculated using available pre-visit measurements in the diary (performed in the week preceding the visit), as defined in Section 15.2.1.3.

Descriptive statistics will be presented by treatment sequence group for actual and change from baseline (week 52 result from MYL-GAI-3001) to scheduled visits for SMBG profile.

Treatment sequence group comparison will be done using the MMRM model, including treatment sequence group, visit, treatment sequence group-by-visit interaction, region, as fixed effects, and baseline values as covariates.

LS means for each treatment sequence group and associated standard errors will be derived. Differences in LS means will be calculated and associated 2-sided 95% confidence intervals (p-value, as required) will be provided. These will be derived from the calculation of Type III sum-of –square and LS means from MMRM model.

For graphical display at each period, LS means and 95% CI for daily mean of SMBG will be generated from the MMRM model including treatment sequence group, treatment sequence group -by-visit interaction, region, as fixed effects, and baseline values as covariates. In addition, mean (± SD) plot for daily mean of SMBG will be prepared for actual measurements by visit.

15.2.3.4. Analysis of Change in Daily insulin dose/unit body weight (daily prandial injectable and basal insulin) for days of 8-point profiles.

Descriptive statistics will be presented by treatment sequence group for actual and change from baseline (week 52 result from MYL-GAI-3001) to scheduled visits for insulin dose including basal insulin dose, daily prandial insulin dose, and total insulin dose.

Treatment sequence group comparison will be done using the MMRM model, including treatment sequence group, visit, treatment sequence group by-visit interaction, region, as fixed effects, and baseline values as covariates.

LS means for each treatment sequence group and associated standard errors will be derived. Differences in LS means will be calculated and associated 2-sided 95% confidence intervals (p-value, as required) will be provided. These will be derived from the calculation of Type III sum-of-square and LS means from MMRM model.

For graphical display at scheduled visits , LS means and 95% CI for total daily insulin dose (meal time +basal) will be generated from the MMRM model including treatment sequence group, visit treatment sequence group-by-visit interaction, region, as fixed effects, and baseline values as covariates. In addition, mean (± SD) plot total daily insulin dose will be prepared for actual measurements by schedule visit.

15.2.4. SUBGROUP ANALYSIS

Not applicable.

16. QUALITY OF LIFE ANALYSIS

Not applicable.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set. All safety output will be presented by treatment sequence group at each treatment period.

17.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using most updated MedDRA central coding dictionary, when it is available at time of analysis is conducted.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with drug administration, whether or not related to the product.

The above definition covers also cases of

- Exacerbation of pre-existing diseases or conditions.
    - Pre-existing diseases or conditions (reported at time of screening in medical history) will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition.

An AE will be defined as treatment emergent (TEAE) if the first onset (or worsening in the case of pre-existing disease) is after the first administration of Mylan's insulin glargine sequence group or Lantus® sequence group (i.e. after the randomization) through 28 days after the last dose.

See Appendix 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of patients for each treatment period within each of the categories described in the sub-section below, will be provided as specified in the templates.

Treatment sequence group comparison will be performed using Fisher's exact test for each treatment period. P-value for the corresponding two-sided test will be presented.

Listings will include TEAEs and Non-TEAEs.

17.1.1. ALL TEAEs

Incidence of TEAEs will be presented for each treatment period by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication.

17.1.1.1. Severity

Severity is classed according to CTCAE v4.03 - Grade 1/mild, Grade 2/moderate, Grade 3/severe, Grade 4/ life-threatening, or Grade 5/Fatal. TEAEs starting after the first dose of study medication with a missing severity will be classified as Grade3/severe. If a patient reports a TEAE more than once within that SOC/ PT/Treatment period, the AE with the highest severity grade will be used in the corresponding severity summaries.

17.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as " Unrelated/not related", "Unlikely related" "possibly related", "probably related" and "definitely related" (increasing severity of relationship). A "related" TEAE is defined as a TEAE with a relationship to study medication as "possibly related", "probably related" and "definitely related" to study medication. TEAEs with a missing relationship to study medication will be regarded as "possible related" to study medication. If a patient reports the same AE more than once within that SOC/ PT/Treatment period, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

All AEs, with the causal relationship to the trial drug reported as "possible", "probable" or "definite" will be considered ADRs. If the relationship to the trial drug is not given, then the AE must be treated as if the relationship were "possible."

17.1.1.3. Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose of the investigation products should be considered adverse drug reactions (ADRs). The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility. All AEs judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to an investigational product will be designated as ADRs.

All AEs, with the causal relationship to the trial drug reported as "possible", "probable" or "definite" will be considered ADRs. If the relationship to the trial drug is not given, then the AE must be treated as if the relationship were "possible."

If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to

study medication will be used in the corresponding relationship summaries.

Frequency and percentage of patients having adverse drug reactions will be presented by treatment sequence group, treatment period, SOC and PT.

17.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the Treatment sequence group withdrawn field in the CRF under "Action taken with IMP/ study medication" or recorded as "Yes" in the CRF under "Did the AE cause the subject to discontinue from the study?".

For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared for each treatment period.

17.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e) CRF. A summary of serious TEAEs by SOC and PT will be prepared for each treatment period.

17.1.4. Adverse Events Leading to Death

TEAEs leading to death are those events which are recorded as "Fatal" on the Adverse Events page of the (e) CRF. A summary of TEAEs leading to death by SOC and PT will be prepared for each treatment period.

17.1.5. Local or Systemic Allergic Reaction

TEAE incidence of both local and systemic allergic reaction will be summarized by SOC and treatment sequence group for each treatment period. A separate listing will also be produced which include only events of local or systemic allergic reaction.

17.2. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry, lipid profile and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol.

Presentations will use SI Units provided the conversion factors and SI Units are shared by sponsor.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Week 52 result from MYL-GAI-3001 trial will be considered as baseline.

The following summaries (descriptive statistics for quantitative measurements and frequency and percentage for qualitative measurements) will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements).
- Incidence of abnormal values according to normal range criteria.
- Shift from baseline according to normal range criteria (for quantitative measurements and/or categorical measurements).
- Shift from baseline according to markedly abnormal criteria (for quantitative measurements and/or categorical measurements).
- Listing of patients meeting markedly abnormal criteria.
- Change from baseline of laboratory measurements will be analyzed using MMRM with model terms of region, treatment sequence group, visit, treatment sequence group-by-visit interaction as fixed effects, and baseline value as covariate. The descriptive statistics for actual measurement and change from baseline along with treatment sequence group comparison will be performed at scheduled visits. LS means for each treatment sequence group and associated standard errors will be derived. Differences in LS means will be calculated and associated 2-sided 95% confidence intervals (p-value, as required) will be provided. These will be derived from the calculation of Type III sum-of-square and LS Means from MMRM model.
- The percentage of patients in categories such as abnormal/non-clinically significant and abnormal/clinically significant will be analyzed using Fisher's exact test. P-value for the two-sided test will be presented.

17.2.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

17.3. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study.

Week 52 result from MYL-GAI-3001 trial will be considered as baseline.

Frequency and percentage of overall assessment of ECG (investigator's judgment) will be presented.

The percentage of patients in categories such as abnormal/non-clinically significant and abnormal/clinically significant will be summarized and treatment sequence group comparison will be performed using Fisher's exact test. The p-value will be presented for the same.

17.4. VITAL SIGNS

The following vital signs measurements will be reported for this study:

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (°C)
- Weight (kg)

The following summaries will be provided for all above vital signs parameters data:

- Actual and change from baseline by visit
- Incidence of markedly abnormal values
- Listing of patients meeting markedly abnormal criteria

Change from baseline (week 52 result from MYL-GAI-3001 trial) of vital sign measurements will be analyzed using MMRM with model terms of region, treatment sequence group, visit, treatment sequence group-by-visit interaction as fixed effects, and baseline value as covariate. The descriptive statistics including actual measurement and change from baseline along with treatment sequence group comparison will be performed at scheduled visits for each period. LS means for each treatment sequence group and associated standard errors will be derived. Differences in LS means will be calculated and associated 2-sided 95% confidence intervals (p-value, as required) will be provided. These will be derived from the calculation of Type III sum-of-square and LS Means from MMRM model.

The percentage of patients in categories such as potentially clinically significant will be analyzed using Fisher's exact test. P-value for the two-sided test will be presented. Descriptive statistics will also be provided as summary tables.

17.4.1. POTENTIAL CLINICALLY SIGNIFICANT CHANGES

Potential clinically significant changes in vital signs measurements will be identified in accordance with the following predefined markedly abnormal criteria

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 160 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 100 mmHg AND change from baseline ≥ 15 mmHg
Heart rate	Bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm

Variable	Unit	Low	High
Body temperature	˚C	NA	≥ 38.3 ˚C AND change from baseline ≥ 1.1 ˚C
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

17.5. PHYSICAL EXAMINATION

Listings will be generated for all physical examination tests.

17.6. OTHER SAFETY ASSESSMENTS

17.6.1. DEVICE SAFETY ASSESSMENT

The device safety assessment will use responses to investigator-administered device questionnaires, and incidence of device-related AEs.

The total incidence of device-related safety events will be summarized with each treatment sequence group both for device-related TEAEs and for events related to device complaints or failures. For device-related TEAEs, two categories will be summarized for each treatment sequence group: needle-related TEAEs such as pain, bruise, and bleeding; and other device-related TEAEs, such as hyperglycemia or hypoglycemia. For confirmed device-related malfunction or failures, incidence will be listed and summarized for each treatment sequence group.

If there are sufficient events of any category, a Fisher exact test will be performed for treatment sequence group comparison. The p-value for the corresponding two-sided test will be presented.

Number and percentage of subjects with device complaints, device complaints leading to dosing error and device complaints leading to an adverse event will be presented.

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17.6.2. IMMUNOGENICITY PROFILES ANALYSES

Following parameters will be summarized for immunogenicity.

- Total Insulin Antibodies
  - Percent Binding (%B/T, Continuous outcome)
  - Positive/Negative (Categorical outcome)
- Cross Reactive Insulin Antibodies
  - Percent Binding (%B/T, Continuous outcome)
  - Positive/Negative (Categorical outcome)

- Insulin(Drug) Specific Antibody
  - Percent Binding (%B/T, Continuous outcome)
- Anti-HCP
  - Positive/Negative (Categorical outcome)

Immunogenicity profiles with continuous variables (% binding) will be analyzed using the MMRM method for each assay, similar to change from baseline efficacy analyses. The model will include the terms region, treatment sequence group, visit, treatment sequence group-by-visit as fixed effects, and baseline value as covariate. The treatment sequence group difference and 95% confidence intervals will be constructed using the model at scheduled visits. In case the normal distribution assumption is severely violated, then non-parametric analysis will be performed using Wilcoxon rank-sum test for treatment sequence group comparison, Hodges Lehmann's estimator will be used to compute the median difference between the treatment sequence groups and the corresponding 95% confidence interval. Safety population will be used for ADA continuous variables. Immunogenicity profiles with dichotomous outcomes will be summarized with frequency and percentage at scheduled visits for each assay. Treatment sequence group comparison will be performed using Fisher's exact test. P-value for the two-sided test will be presented.
Correlation analyses of insulin cross-reactive antibodies with clinical factors such as HbA1c and insulin doses will be performed by treatment sequence group along with graphics to explore relationship of insulin antibodies with such factors for each assay method used. Additionally, mean (±SD) and median (IQR) for actual measurements by visit will also be presented.
Regression plots will be produced to assess the consistency of results obtained between the two assay types, and the regression plots will be produced for Total Insulin Antibody, Cross Reactive Insulin Antibody and Insulin (Drug) Specific Antibody by treatment sequence group.

The incidence of patients with increase over 10% cross reacting antibody increase in both assays, of HbA1c over 0.2% increase and insulin dose increase at any visit will also be summarized descriptively (for categorical measures) together to explore treatment sequence group difference.

An individual data listing will be provided for the patients with increase over 10% cross reacting antibody increase in both assays, of HbA1c over 0.2% increase and insulin dose increase at Week 12, 24 and 36.
The observed and Change values of HbA1c, Insulin dose, Cross reactive antibodies (Both assays) Fasting blood glucose, Subject's age, Duration of diabetes and Adverse events reported will be presented in the listing.

Presence of anti-HCP antibodies in samples from patients will be assessed using a validated immunoassay method. The results will be presented as positive or negative from anti-HCP antibodies based on the samples that HCP assay was done. Frequency and percentage of presence of anti-HCP antibodies will be presented at scheduled visits by treatment sequence group. The p-value from Fisher's exact test will be presented to test the difference between the treatment sequence groups for scheduled visits.

17.6.3. HYPOGLYCEMIA ANALYSES

Hypoglycemia is a state produced by a lower than normal level of glucose in the blood. Hypoglycemia is classified as severe, documented symptomatic, asymptomatic, probable symptomatic, relative, or nocturnal hypoglycemia. The details of Classification can be found in protocol Sections 7.4.8 and 7.5.6.1.

Patients will be instructed to record all hypoglycemic events in the patient diary from visit 2 until the EOT visit. The hypoglycemic events will be reviewed by the investigator and transcribed into the eCRF by the investigator or designee after the diary has been collected.

Hypoglycemia rate per patient per 30 days calculated between two visits is defined as total number of episodes between two visits divided by the number of days between the visits, multiplied by 30 days. This rate will also be calculated per patient for nocturnal hypoglycemia episodes.

Hypoglycemia rate per patient per 30 days will be analyzed at all scheduled visit using MMRM method similar to the continuous efficacy variables at scheduled visits. The model will include the terms region, treatment sequence group, visit, visit-by-treatment sequence group as fixed effects, and baseline value as covariates. The rate per patient per 30 days calculated between two visits is defined as total number of episodes between two visits divided by the number of days between the visits, multiplied by 30 days. This rate will also be calculated per patient for nocturnal hypoglycemia episodes. In case the normal distribution assumption is severely violated, then non-parametric analysis will be performed using Wilcoxon rank-sum test for treatment sequence group comparison, Hodges Lehmann's estimator will be used to compute the median difference between the treatment sequence groups and the corresponding 95% confidence interval.

Due to the uneven visit intervals for scheduled visits, additional exploratory analyses for hypoglycemia rate per patient per 30 days based only on the SMBG week (during the week the SMBG is done) for each visit will be performed using same method as above.

The similar analysis will be done for asymptomatic hypoglycemia rate separately based only on SMBG week and none SMBG week.

For change from baseline of hypoglycemia rate, for graphical display at scheduled visits, LS means and 95% CI will be generated from the MMRM model. Additionally, mean (±SD) and median (IQR) for actual measurements by visit will also be presented.

The incidence of hypoglycemic episodes during a time period on treatment is defined as the incidence of patients with at least one hypoglycemic episode occurring within that period of time. Incidence of hypoglycemic episodes will be presented by treatment sequence group, visit and overall. Incidence of hypoglycemic episodes will also be summarized by category (Severe Hypoglycemia, Documented Symptomatic Hypoglycemia, Asymptomatic Hypoglycemia, Probable Symptomatic Hypoglycemia, Relative Hypoglycemia and Nocturnal Hypoglycemia). The detailed definition of each type of hypoglycemic event is mentioned in the protocol Section 7.5.6.1.

In addition, nocturnal hypoglycemia rate and incidence will be analyzed in a same way as overall hypoglycemic episodes

Listings of hypoglycemic episodes and severe hypoglycemic episodes will be presented by visit for each patient. If a sufficient number of severe hypoglycemic episodes are reported, then incidence summaries similar to the incidence of hypoglycemic episodes will be included.

18. DATA NOT SUMMARIZED OR PRESENTED

Not Applicable

19. REFERENCES

Dobson, A. J. (2002). *An introduction to generalized linear models, 2nd ed.* Chapman & Hall/CRC.

Little, R., & Yau, L. (1996). Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. *Biometrics* , vol 52, 1324-1333.

APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 2. MAJOR PROTOCOL DEVIATIONS

The major protocol deviations are defined in the following table:

PD header as per Protocol	Specific example database
Patient not meeting the following selection criteria (inclusion and exclusion) at screening but still included in the study	Patients recruited in to the study violating the selection criteria Insulin was initiated only after 6 months of T1DM diagnosis Patient was on basal-bolus insulin therapy for at least 1 year before screening Patient was on once daily Lantus® at stable dose Lab criteria Efficacy criteria - HbA1c Safety criteria - ECG, Eye testing, Safety lab tests, Hb, LDL, TG, ALT, AST, Creatinine, Vital signs, HT Other criteria - C peptide, BMI, infectious samples, drug abuse, Insulin resistance, age
Patient continued in the study despite meeting study discontinuation criteria	Protocol specified withdrawal criteria Withdrawal of consent Use of prohibited medications [insulin, insulin analogs and other anti-diabetes medications as well as glucocorticoid therapy (oral, intravenous, inhaled or other routes that produce systemic effects)] For female patients, diagnosis of pregnancy or a stated intention to become pregnant. Repeated non-compliance as determined by the investigator in a consolidated overall evaluation of compliance At the investigator's discretion, for safety issues such as severe hypoglycemia or hypoglycemic unawareness. At the investigator's discretion, in certain situations such as significant intercurrent illness, hospitalization for surgery, or an SAE which in the opinion of the investigator warrants withdrawal.
Failure to perform tests or procedures which will impact the interpretation of key endpoints of the study	HbA1c not tested at screening, randomization, 12th and 24th week visit (all missed)
Patient not following treatment regimen mentioned in the protocol	Patient was not given the assigned IP (instead of test medication, comparator medication was given) Using insulin Glargine that is not IMP and part of the study during the study period
Study procedure issue	Study completed without signing ICF Sponsor unapproved IP used (temperature or humidity excursion prove. For a patient recruited from Germany, Name, date of birth, or information

	revealing patient identify was captured and it is not acceptable as per the German law