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16.1.9 Documentation of statistical methods

Statistical Analysis Plan V1.0, 04 May 2018

Statistical Analysis Plan V2.0, 18 October 2018

STATISTICAL ANALYSIS PLAN

MYL-1501D-3004

A RANDOMIZED, MULTI-CENTER, DOUBLE-BLIND, PARALLEL-GROUP CLINICAL STUDY COMPARING THE EFFICACY AND SAFETY OF MYL-1501D PRODUCED BY TWO MANUFACTURING PROCESSES IN TYPE 1 DIABETES MELLITUS PATIENTS.

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 04MAY2018) for Protocol MYL-1501D-3004 V2.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	04MAY2018	Irene Dehem	Not Applicable – First Version

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical (class)
BDR	blind data review
BMI	Body Mass Index
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference of Harmonization
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MAR	missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	mixed model for repeated measures
PP	Per Protocol
PT	Preferred Term
RND	randomized population
SAE	serious adverse event
SAF	Safety
SAP	statistical analysis plan
SE	standard error
SMBG	Self Monitored Blood Glucose
SOC	System Organ Class
TEAE	treatment emergent adverse event
T1DM	type 1 diabetes mellitus
WHO-DD	World Health Organization – Drug Dictionary (enhanced)

2. 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-3004. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol amendment 1 (dated 11JAN2018).

3. STUDY OBJECTIVES

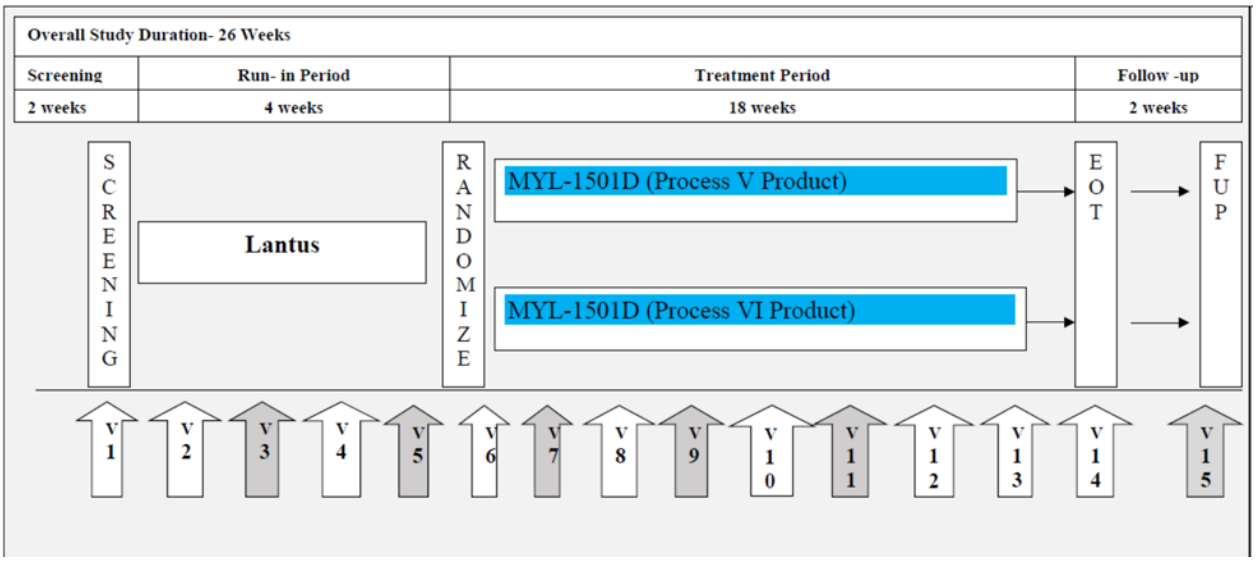
The primary objective is to test whether MYL-1501D product from Process VI once daily is non-inferior to MYL-1501D product from Process V once daily based on the change in HbA1c from baseline to week 18 when administered in combination with mealtime insulin lispro.

3.1. OTHER OBJECTIVES

The other objectives are to compare MYL-1501D product from Process VI and Process V at week 18, when administered in combination with mealtime insulin lispro, with respect to:

- Immunogenicity: incidence and change from baseline in the relative levels of anti-drug antibody
- Hypoglycemic events: incidence and rate per 30 days
- Occurrence of local reactions, systemic reactions and other adverse events
- Device-related safety assessment
- Change in fasting plasma glucose from baseline
- Change in insulin dose per unit body weight (U/kg) from baseline
- Change in 8-point Self-Monitored Blood Glucose (SMBG) profile from baseline

4. STUDY DESIGN



4.1. GENERAL DESCRIPTION

This is a multicenter, double-blind, randomized, parallel-group phase 3 study in patients with type 1 diabetes mellitus (T1DM) comparing the efficacy, immunogenicity and safety of MYL-1501D products from two manufacturing processes (Process V and Process VI). A total of 202 patients with T1DM are planned to be randomized in a 1:1 ratio between MYL-1501D Process V and MYL-1501D Process VI. Approximately 110 sites will be included in the study.

After up to 2-week screening period, all patients will be titrated on Lantus® during a 4-week run-in period, and will be shifted from their current mealtime insulin to Humalog®. The patients will be randomized (stratified by investigational site and time of administration of glargine [morning and evening]); one group will receive MYL-1501D product from Process V, while the other group will receive MYL-1501D product from Process VI for 18 weeks. A follow-up visit will be scheduled 2 weeks after last dose of MYL-1501D.

The none-hypothesis is that the upper bound of treatment difference (Process VI minus Process V) is over 0.4 and alternative hypothesis is that upper bound of treatment difference is less than or equal to 0.4.

Patients will remain blinded until the database is locked, then an unblinding request form will be sent to the IVR provider in order to get the randomization code. Any analyses done prior to database lock will use dummy treatments.

4.2. SCHEDULE OF EVENTS

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									F-U
Study Visits[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT)	V15 (FU)
Study Week	-6 to -4	-4	-3	-2	-1	0	1	2	4	6	9	12	15	18	20
Study Days	-42 to -28	-28±3	-21±3	-14±3	-7±3	0±3	7±3	14±3	28±3	42±3	70±7	84±7	112±7	126±7	140±7
Informed Consent	x														
Inclusion/Exclusion Criteria Review	x					x									
History of previous insulin usage	x														
Dilated Ophthalmoscopy / retinal photography if not done in the last 6 months	x														
Standard-of-care specifics[2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Age, Gender, Height, Race	x														
Body Weight and BMI	x					x		x		x		x		x	
Pregnancy Test[3]	x					x		x		x		x	x	x	
Medical History including concomitant illness	x														
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vitals signs measurement (sitting)	x	x		x		x		x		x		x		x	
Physical examination	x					x								x	
12-lead ECG (supine)	x					x								x	
Randomization						x[8]									
Record AEs and SAEs (including local and systemic allergic reactions) and hypoglycemic events[4] due to medication, disposable pen or needle		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record device safety information			x	x	x	x	x	x	x	x	x	x	x	x	

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									F-U
Study Visits[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT)	V15 (FU)
Study Week	-6 to -4	-4	-3	-2	-1	0	1	2	4	6	9	12	15	18	20
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Fasting plasma glucose	x	x		x		x		x		x		x		x	
HbA1c Assay	x					x						x		x	
Fasting C-peptide, HIV, HBsAg, and HCVAb	x														
Sampling for hematology, blood chemistry and urinalysis[5]	x					x								x	
Fasting lipid profile	x					x						x		x	
Sampling for immunogenicity [9]	x					x		x		x		x		x	
Sampling for PK[6]						x		x		x		x		x	
Review 8-point SMBG Profile performed in the week before the visit [7]			x	x	x	x				x		x		x	
Dose review of Lantus, MYL-1501D and insulin lispro and instruction		x	x	x	x	x	x	x	x	x	x	x	x	x	
Dispense Study Medication and ancillary supplies		x				x				x		x			
Drug Accountability and Compliance				x		x		x		x		x	x	x	
Dispense subject diary		x				x				x		x			
Review subject diary				x		x				x		x		x	

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

No changes.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

5.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC or interim analysis for this study.

5.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this SAP, Sponsor Authorization of Analysis Sets, Database Lock and Unblinding of Treatment.

6. ANALYSIS SETS

Agreement and authorization of patients included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

6.1. ALL PATIENTS SCREENED

The all patients screened population is defined as all patients who consent for the study.

6.2. RUN-IN POPULATION

The run-in population is defined as all patients who consent for the study and entered into the run-in phase. The patients in this population will be summarized under the total number of patients. Run-in failure patients will be summarized under the category of “run-in failure”.

6.3. ALL PATIENTS RANDOMIZED POPULATION [RND]

The all patient randomized (RND) population will contain all patients got randomized to study medication. The patients who discontinue the study during run-in period will not be included in the randomized population.

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

6.4. INTENT-TO-TREAT POPULATION [ITT]

The Intent-to-Treat (ITT) population includes all randomized patients (including patients who receive incorrect treatment, do not complete the trial or do not comply with the protocol).

The patients under the ITT population will be analyzed according to the planned treatment group.

All primary and secondary efficacy analysis will be based on the ITT population.

6.5. SAFETY POPULATION [SAF]

The safety population (SAF) will contain all patients who are randomized and take at least one dose of study drug.

The safety analysis will be conducted according to the treatment received. If there is any doubt whether a patient was treated or not, they will be assumed treated for the purpose of the analysis.

6.6. PER PROTOCOL POPULATION [PP]

The per-protocol population (PP) will contain all patients who complete week 18 and have HbA1c3 measurements as per the protocol, or have at least one post-baseline HbA1c data for patients who discontinue prematurely, and do not have protocol deviation that impact the primary outcome. Patients who meet rescue medication criteria and take rescue medication will be excluded from the PP. The list of deviations leading to exclusion from the PP population will be identified, reviewed and documented prior to DB lock and determined in the blind data review meeting and documented in the blind data review report prior to the database lock. The subjects who are excluded from PP population and reason for exclusion will be listed.

7. GENERAL CONSIDERATIONS

7.1. 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 randomization, (Day 1 is the day of randomization).

- 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.

7.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to receiving randomized treatment reference (day of randomization) start date (including unscheduled assessments). In the case where the last non-missing measurement and the randomized treatment start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the randomized treatment start date will be considered post-baseline.

For insulin (mealtime, basal and total) levels, baseline is the value collected at Visit 6 (Week 0) which correspond to values collected prior injection of study medication.

7.3. 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 scheduled visit if scheduled visit value is missing or the Last Observation Carried Forward (LOCF) value in case primary sensitivity analysis, or best/ worst case value where required (e.g. shift table) in safety analysis.

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 entered under the Visit 14 (week 18), but for summary tables it will be mapped to the next available planned visit number after their last scheduled visit. For example, should a patient discontinue at Visit 9, the Early Termination visit will have their Fasting plasma glucose and their HbA1c assay taken. The fasting plasma glucose would then be summarized under Visit 10 and the HbA1c under Visit 12.

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

7.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

7.5. STATISTICAL TESTS

The default significant level will be (5%); confidence intervals will be 95% and all tests will be two-

sided, unless otherwise specified in the description of the analyses.

Non-inferiority will be tested at 2.5% (one-sided) level of significance.

7.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

7.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

8. STATISTICAL CONSIDERATIONS

8.1. 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.

- Pooled sites
- Time of Glargine administration (morning, evening), stratification factor.
- Baseline HbA1c (continuous variable)

8.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers in the USA.

When specified, statistical analysis will be adjusted for pooled sites based on US census regions.

All sites within a US census region (northeast, midwest, south, west, pacific) with fewer than 8 randomized patients will be combined into a single pooled site for analysis purposes.

The pooled method will be as follow (performed manually):

Step 1: All sites within a US census region with fewer than 8 patients will be combined into a single pooled site. If the resulting pooled site still has fewer than 8 patients, then proceed to the next step.

Step 2: The pooled site (<8) will be further combined with the smallest unpooled site within that region. If there is not another unpooled site within that region, then proceed to the next step.

If several unpooled sites within the region have the smallest patients, the preference is to select the unpooled site that is the closest to the site in distance.

If there are still more than one unpooled site within the region after evaluating the distance, an unpooled site will be selected randomly to combine with the pooled site (<8) from Step 1.

Step 3: The pooled site will be combined with the smallest pooled site from another region (that is the closest in distance).

The treatment by pooled-site interaction will be tested in the primary efficacy model. Where there is evidence of an interaction ($p<0.10$), graphical inspection of descriptive statistics will be used to assess whether the interaction is quantitative (i.e. the treatment effect is consistent in direction but not size of effect) or qualitative (i.e. the treatment is beneficial for some but not other regions).

8.3. MISSING DATA

After having mapped data captured at unscheduled and/or early termination visits (if any) to schedule missing visits using visit windows technique (refer to section 7.4), missing primary data will be imputed by using the multiple imputation (MI) technique (see section 16.1.3).

As another sensitivity analysis, the imputed values by MI will be corrected such that the full non-inferiority margin will be added for imputed values in Process VI group.

A sensitivity analysis using Last Observation Carried Forward (LOCF) will also be performed on the primary efficacy parameter.

In the secondary efficacy data, the weight used in the daily total insulin will be imputed by the weight of the previous visit value if current weight value is missing.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustment for multiplicity will be performed.

8.5. ACTIVE-CONTROL STUDIES INTENDED TO SHOW NON-INFERIORITY OR EQUIVALENCE

Non-inferiority will be established if the upper bound of a two-sided 95% confidence interval (CI) for the absolute difference (MYL-1501D Process VI minus Process V) of mean change from baseline to week 18 for HbA1c is less than or equal 0.4%.

8.6. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the exploratory analysis sections. It should be noted that the study was not designed to detect treatment differences with high statistical power

within subgroups.

The following subgroups will be assessed and described within the subgroup analysis sections (16.2.4). A minimum of 8 subjects/arm in each subgroup is needed. For subgroup with less than 8 subjects/arm, this subgroup will be pooled with the other ones having less than 8 subjects/arm together and the subgroup will be named "other" if there are other subgroups with less than 8 subjects/arm exist.

- Gender:
  - Female
  - Male
- Age (years):
  - ≤ 21
  - > 21 to <65
  - ≥65
- Race in 5 categories:
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
- Ethnicity in 2 categories:
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not reported or Unknown

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

10. 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 week 18 or discontinued early as well as completed the trial will be summarized for each treatment group. Reason for

discontinuation during week 18 will be summarized. The summary of reason for discontinuation from the study will also be presented.

The number and proportion of patients withdrawing the study during the run-in phase will be presented. The number and proportion of patients in each population will also be summarized.

A listing of patients who fail the inclusion/exclusion criteria will be produced.

A summary of major protocol deviations will be provided as frequency and percentages. Protocol deviations in the run-in phase will be summarized separately. A list of all major protocol deviations will also be provided.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the RND and SAF populations.

The continuous demographic/baseline variables will be summarized using the mean, median, standard deviation, minimum, and maximum values. For categorical (nominal) variables, the number and percentage of patients will be used. No statistical testing will be carried out for demographic or other baseline characteristics. All demographic and baseline characteristics will be presented in a listing.

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

- Age (years) - calculated relative to date of informed consent
- Gender
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Duration of diabetes (years)
- Time of glargine administration (morning, evening)
- Baseline fasting plasma glucose (mmol/L)
- Baseline HbA1c (%)
- Insulin use prior to screening (yes, no)

- Fasting C-Peptide, HIV, HBsAg and HCVAb (positive, negative)

11.1. DERIVATIONS

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

12. MEDICAL HISTORY

Medical History information will be presented for the SAF and coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 20. Coded medical history terms will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group. Multiple entries for an individual patient under same SOC/PT will only be counted once.

13. MEDICATIONS

Medications will be presented for the SAF and coded using WHO Drug dictionary 01SEP2017.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the reference start date.
- Insulin use prior first dose are any insulin medication used prior to screening visit.
- 'Concomitant' medications are medications which:
  - started prior to, on or after the randomization date
  - AND ended on or after the randomization date of study medication or were ongoing at the end of the study.

Prior and concomitant medication will be summarized by treatment group. The number of patients taking each medication will be presented by Anatomical Therapeutic Chemical (ATC) names (levels 1, 2, 3). Each patient taking the same therapy more than once will be counted once within each ATC code level. All prior and concomitant medications will be presented in data listing. A separate listing on prohibited medications will also be provided.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for the SAF.

The exposure will be summarized for each treatment group using the mean, standard deviation, median, minimum and maximum. Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

14.1. DERIVATIONS

Duration of exposure days = date of last study medication administration minus the date of reference day + 1.

Where the reference start date is defined in section 6.1 and the date of last study medication will be taken from the "End of Treatment" form.

15. STUDY TREATMENT NON-COMPLIANCE

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

- Missing total meal time insulin daily since last visit
- Missing basal insulin daily since last visit
- Took two times more basal insulin daily since last visit
- Took less or more than prescribed basal insulin dose units daily since last visit

Number and proportion of patients with non-compliance will be summarized along with individual categories of non-compliance for each category.

The non compliance proportion is defined as total accumulative non-compliant days/duration of treatment exposure in days. Summary of non-compliance proportion will be performed by each non-compliance category for each treatment group. The treatment groups will be compared by using an ANOVA model which will include treatment and pooled-site.

16. EFFICACY OUTCOMES

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY VARIABLE

The primary efficacy variable is change in HbA1c from baseline to week 18 for the ITT population.

The HbA1c is collected by central laboratory Q2Solutions.

16.1.2. MISSING DATA METHOD FOR PRIMARY EFFICACY VARIABLE

After having mapped data captured at unscheduled and/or early termination visits (if any) to schedule missing visits using visit windows technique (refer to section 7.4), MI will be used for the primary efficacy analysis. Refer to section 16.1.3 for more details.

If subjects initiate rescue medication after Week 12, HbA1c value at Week 18 will be considered as missing and imputed as described above i.e., first remapped data collected at unscheduled/early termination visits (if any) to Week 18 and then, use MI to impute remaining Week 18 data.

16.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

Descriptive statistics will be tabulated by treatment and by time point of the actual HbA1c value and the changes from baseline.

The primary objective of this study is to test the hypothesis that MYL-1501D product from Process VI is non-inferior to MYL-1501D product from Process V based on change in HbA1c from baseline to week 18.

The primary efficacy analysis will be performed for the ITT analysis set.

Mean changes from baseline in HbA1c will be analyzed based on all observed data of schedule visits as well as data imputed using the unscheduled/early termination data (if collected) or MI methodology for schedule visits at which no value is captured (refer to section 16.1.2).

MI will be performed under the assumption of missing-at-random (MAR) and will be implemented in two steps.

First, partial imputation assuming MAR will be carried out to impute intermittent (non-monotone) missing data based on multivariate joint Gaussian imputation model using the Markov chain Monte Carlo (MCMC) method. A separate model will be used for each treatment group. The imputation model will include the pooled investigator sites and basal insulin dose time (morning vs. evening) as fixed covariate and observed HbA1c values at baseline (visit 6), week 12 (visit 12) and week 18 (visit 14). The MCMC method in the MI procedure in SAS will be used with multiple chains, 200 burn-in iterations, and a non-informative prior. In case of non-convergence or non-estimability issues, a ridge prior and single model will be considered with treatment group added as explanatory variable to model.

Then, the remaining monotone missing data will be imputed using sequential regression multiple imputation, where a separate regression model is estimated for imputation of each variable (i.e., measurement at each visit) one after the other including the observed values and the values just imputed from the previous visit. Each regression model will include explanatory variables for pooled investigational sites, basal insulin dose time (morning vs. evening), treatment group and all previous (baseline (visit 6), week 12 (visit 12) and week 18 (visit 14)) values of HbA1c.

No rounding or range restrictions will be applied.

Imputed data will consist of 100 imputed datasets. The random seed number for the partial imputation with the MCMC method will be 20171220, and the random seed number for the sequential regression MI will be 171016.

Each of the 100 imputed datasets will be analyzed using the following analysis method. Change from

baseline in HbA1c to each post-baseline visit will be calculated based on observed and imputed data. Mean changes from baseline in HbA1c values will be analyzed using a mixed model for repeated measures (MMRM) approach. Restricted maximum likelihood (ReML) estimation will be used. The MMRM model will include the changes from baseline in HbA1c values as dependent variables, the baseline HbA1c values as fixed covariate, pooled investigational sites, basal insulin dose time (morning vs evening), treatment group (MYL 1501D Process V and MYL 1501D Process VI), visit (week 12 and week 18), and treatment group by visit interaction as fixed effects, and subjects as random effect. An unstructured covariance structure will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. If this analysis fails to converge, the following covariance structures will be tested: AR(1), ARH(1), CS, CSH, TOEP, TOEPH. The covariance structure converging to the best fit, as determined by Akaike's information criteria (AIC) will be used as the primary analysis.

Treatment group comparison at week 18 will be based on the least square mean (LS mean) difference between treatment groups (i.e., MYL 1501D Process VI – MYL 1501D Process V) in change from baseline in HbA1c estimated by the model in each imputed datasets. Results from analysis of each imputed dataset i.e., LS mean differences and their standard error (SE), will be combined using the Rubin's imputation rules to produced pooled LS mean estimate of treatment difference and its 2-sided 95% confidence interval (CI).

Non-inferiority will be established if the upper limit of the two sided 95%CI for the difference (MYL-1501D Process VI minus Process V) of mean change from baseline to endpoint for HbA1c is not greater than 0.4% at week 18.

Refer to APPENDIX 3 for SAS code example.

For graphical display at scheduled visits, the LS Means and 2-sided 95% CI for the changes from baseline in HbA1c to week 12 and week 18 obtained from the MMRM model will be presented by treatment group. Similar graphical display will be presented for the mean actual HbA1c values and SD over time by treatment group.

16.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

- Sensitivity to analysis set: the PP population will be used with the same MMRM model described above to establish non-inferiority.
- Sensitivity to missing data assumptions:
    - Same analysis approach as the primary analysis, but without imputing missing values. This will be analyzed based in ITT.
    - In another method, the same analysis approach as the primary analysis will be performed, but the imputed values will be corrected such that the full non-inferiority margin will be added for imputed values in Process VI group. This will be analysed based on ITT.
    - In a third sensitivity analysis, tipping-point analysis will be performed using an algorithm proposed by Yan et al (2009) to explore the robustness of the results with regard to a bias against the Process VI treatment arm and in favour of the Process V treatment arm. In order to quantify the bias (k), scenario 2 of the Yan et al (2009) algorithm will be used. Missing Week 18 values will have the value k (positive) added to the Process

VI arm (worsening results) and subtracted from the Process V arm (improving results). The value for k is determined by adjusting the bias in an MNAR version of starting with a value of 0.01 and increasing it until the MNAR version of the MI method described in Appendix 4 meets or surpasses the non-inferiority margin. That is the upper limit of 95% interval of treatment difference is > =0.4 (p-value for test non-interiority is >=0.05). The seed and code for this process are detailed in Appendix 4. The shift parameter as well as summary statistics for the MI model with the tipping point adjustment of k will be reported.

- As a final sensitivity analysis, missing data will be imputed by using LOCF. An ANCOVA model will be used on the change from baseline in HbA1c to month 18. The model will include treatment (2 levels: MYL-1501D Process V and MYL-1501D Process VI) as fixed effect, the baseline HbA1c as covariate, and patient as random effect. The pooled sites and basal insulin dose time (morning or event) will also be included in the model as fixed effects. This will be analyzed on ITT and PP.
- In addition, the means for each treatment and difference between treatments for missing data at Week 18 will be summarized for all sensitivity analyses.

16.2. SECONDARY EFFICACY

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

16.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.2.1.1. Fasting plasma glucose

The fasting plasma glucose is collected at baseline, week 2 (visit 8), week 6 (visit 10), week 12 (visit 12) and week 18 (visit 14, End of Treatment). The measurements are performed by the central laboratory Q2.

Actual values and changes from baseline at each time point will be computed and summarized by treatment group.

A separate analysis will be performed excluding patients with no fasting status.

16.2.1.2. Daily insulin dose per unit body weight (mealtime, basal insulin and total) for days of 8-point profiles

Patients will be asked to document the dose of insulin taken on the same day they will perform the 8-point SMBG profiles (from week -3 to week 18). The measurements are taken the week prior to the visits, so the week prior to:

- Week -3 (Visit 3)
- Week -2 (Visit 4)
- Week -1 (Visit 5)

- Week 0 (Visit 6)
- Week 6 (Visit 10)
- Week 12 (Visit 12)
- Week 18 (Visit 14)

Doses will be recorded in the patient's 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 doses variables: meal time insulin dose, basal insulin and total insulin dose.

Daily Meal time insulin dose: is the sum of all the total daily meal time insulin (Humalog) dose over the double-blind treatment period divided by the number of days measured. For the computation of total daily mealtime doses, only the patients with at least three mealtime doses at a particular day are considered. That is, total daily mealtime dose will not be computed for a day if the mealtime dose is recorded less than 3 times for that day.

Daily Basal insulin dose: is the average of the insulin dose over days measured during the double-blind period.

Daily Total insulin: is the sum of all total daily meal time doses and all basal insulin doses over the double-blind treatment period divided by the number of days measured. Similarly to total daily mealtime dose for which less than 3 mealtime doses are recorded, the missing insulin doses will not be considered for the average computation. That is, if either the mealtime doses are recorded less than 3 times or the basal insulin dose is missing for a particular day of collection, total insulin dose will not be computed. The total insulin dose will be computed for the remaining days where basal insulin dose and at least 3 mealtime doses are collected.

All doses will be divided by total body weight (kg) to convert to daily insulin dose (U) per unit body weight (kg). If body weight at that visit is missing, the weight from previous visit will be used.

16.2.1.3. 8-point Self-Monitored Blood Glucose (SMBG) profile

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 3 days, 2 should be consecutive). The patient should document the 3 pre-visit measurements in the diary.

The following summaries will be summarized at week 6, 12, and week 18:

Individual 8-points SMBG:

The over 3 day averages will be performed for the measures taken at:

- Before breakfast
- Two hours after breakfast
- Before lunch
- Two hours after lunch

- Before dinner
- Two hours after dinner
- Just before sleep
- At 3:00 AM

Averages will be performed at each visit.

Excursions and averages in SMBG:

The following averages will be computed:

- Morning excursion
- Noon excursion
- Evening excursion
- Overall excursion
- Pre-meal average
- Post-meal average
- (4-point average) pre-meal and bedtime average
- Overall average

The 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 the overall excursion at morning, afternoon and evening, the individual excursion values obtained on each day will be averaged across the three days.

To compute the overall excursion, first the average of the morning, noon and evening excursion within a day will be computed, then the average will be done across the 3 days.

The pre-meal average will be the average of the following timepoints: before breakfast, before lunch, before dinner on each day, then the average will be done over the 3 days.

The post-meal average will be the average of the following timepoints: two hours after breakfast, two hours after lunch, two hours after dinner on each day, then the average will be done over the 3 days.

The pre-meal and bedtime average will be the average of the following timepoints: before breakfast, before lunch, before dinner, just before sleep, then the average will be done over the 3 days.

The overall average will be the average of all the 8 timepoints during a day. The daily average will not be computed for a day if more than 3 timepoints are missing on a particular day. The overall average will be kept missing if the daily average is missing for all three days. If the average is missing for one or two days, the average of the remaining days will be considered for the computation.

16.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE(S)

Imputation will be performed for the SMBG and weight for dose calculation as described in section 16.2.1.

16.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

16.2.3.1. Analysis of change from baseline in HbA1c at scheduled visits

Descriptive statistics will be presented for actual and change from baseline to scheduled visits for HbA1c.

Treatment group comparison will be done using the MMRM model as used for the primary endpoint (without imputing the missing values), including treatment, visit, treatment-by-visit interaction, pooled-investigator, basal insulin dosing time, as fixed effects, baseline values as covariate and subjects as random effect.

LSMeans for each treatment group, as well as associated SE and 2-sided 95% CI will be provided by visit. Differences in LSMeans will be calculated and associated 2-sided 95% confidence intervals and p-values will be provided for each visit.

16.2.3.2. Analysis of change from baseline in fasting plasma glucose

Descriptive statistics will be presented for actual and change from baseline to scheduled visits for fasting plasma glucose. A separate analysis will be done with excluding data with non-fasting status.

Treatment group comparison will be done using the MMRM model as used for the primary endpoint (without imputing missing values), including treatment, visit, treatment-by-visit interaction, pooled-site, basal insulin dosing time, as fixed effects, baseline values as covariate and subjects as random effect.

LSMeans for each treatment group, as well as associated SE and 2-sided 95% CI will be provided by visit. Differences in LSMeans will be calculated and associated 2-sided 95% confidence intervals and p-values will be provided for each visit.

For graphical display at scheduled visits the mean and SD plot will be prepared for the actual plasma glucose measurement by visit and treatment group; LSMeans and 2-sided 95% CI from the same MMRM model will similarly be displayed graphically.

16.2.3.3. Analysis of Change in Daily insulin dose per unit body weight (mealtime, basal insulin and total) for days of 8-point profiles.

Descriptive statistics will be tabulated by treatment and by timepoint. Change from baseline to post-baseline timepoints will also be presented for insulin dose including daily basal insulin dose, daily meal time insulin dose, and daily total insulin dose.

These secondary efficacy parameters will be analyzed using the same MMRM model as the primary efficacy analysis (without imputing missing values). Estimates of the means, LSMeans (2-

sided 95% CIs) as well as treatment difference at each visit will be presented.

A graphical display at scheduled visits with the mean and SD plot will be prepared for each of these secondary efficacy endpoints by visit and treatment group; LSMeans and 2-sided 95% CI from the same MMRM model will similarly be displayed graphically.

16.2.3.4. 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).

Descriptive statistics will be presented for the actual and change from baseline to scheduled visits for SMBG profile.

Treatment group comparison will be done using the same MMRM model as the primary efficacy analysis (without imputing missing values). Estimates of the means, LSMeans (2-sided 95% CIs) as well as treatment difference at each visit will be presented.

For graphical display at scheduled visits the mean and SD plot will be prepared for the actual Overall SMBG average measurement by visit, LSMeans and 95% CI from the same MMRM model will similarly be displayed graphically.

16.2.4. SUBGROUP ANALYSIS

The effect of subgroups mentioned in section 8.6 on the change from baseline HbA1c at week 18 will be examined by employing a MMRM model. The subgroups will be included in the model along with the treatment group. Additionally separate subgroup analysis within each subgroup mentioned in section 8.6 will be performed same MMRM model for treatment comparison within each subgroups.

The similar subgroups will also be examined for the immunogenicity parameters for the percent binding and the incidence analysis of cross reactive antibody. Besides examine subgroup by treatment interaction for percent binding. Separate analysis for both percent binding and incidence will be performed for treatment comparison within each subgroup.

16.3. EXPLORATORY PK ANALYSIS

Exploratory PK analysis will be performed by Mylan PK/DM department.

Descriptive statistics of PK concentration values will be presented for each scheduled visits by treatment group.

Treatment group comparison will be done using the GLM model on log-transformed PK concentration values including treatment, visit, treatment-by-visit interaction, time of administration of glargine [morning and evening], all as fixed effects. If treatment-by-visit interaction is not significant, this term will be dropped from the model, the reduced model will be performed to produce the final analysis. If treatment-by-visit interaction is significant, then this interaction term and visit term will be drop from the model and final model will be performed by visit with only treatment and time of administration in the model.

LSMeans for each treatment group and Geometric Mean Ratio between the treatment groups will be calculated. 2-sided 90% confidence intervals for the log transformed treatment difference and p-values will be provided.

17. QUALITY OF LIFE ANALYSIS

Not applicable.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set. Percentages will be computed on the total number of subjects in each treatment group.

18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 20.1.

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.

Events occurring in patients treated with the active comparator are also considered AEs.

An AE will be defined as treatment emergent (TEAE) if the first onset (or worsening in the case of pre-existing disease) is after randomization through follow-up visit or 14 days after last dose [for patients that do not have a follow-up visit].

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 within each of the categories described in the sub-sections below, will be provided as specified in the templates.

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

Listings will include TEAEs and Non-TEAEs.

18.1.1. ALL TEAEs

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

18.1.1.1. Severity

Severity is classed as mild/ moderate/ severe/ life-threatening/ death (increasing severity). TEAEs starting on or after the first dose of study medication with a missing severity will be classified as severe. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

18.1.1.2. Adverse Drug Reaction (Relationship to Study Medication)

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 reaction will be presented by treatment, SOC and PT.

18.1.2. TEAEs LEADING TO DISCONTINUATION OF STUDY MEDICATION

TEAEs leading to permanent discontinuation of study medication will be identified by using the Treatment withdrawn field in the CRF under "Action taken with study medication".

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

18.1.3. 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.

18.1.4. 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.

18.1.5. LOCAL OR SYSTEMIC ALLERGIC REACTION

The local and systemic allergic reactions are recorded on the adverse events page of the eCRF.

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

18.1.6. DEVICE-RELATED ASSESSMENT

The relationship to the insulin glargine pen/needle and to the Humalog pen/needle are recorded on the adverse events page of the eCRF.

TEAE incidence will be summarized by SOC and treatment group for the insulin glargine pen/needle relationship and for the humalog pen/needle relationship and for both.

The incidence of device problems (even if not leading to an AE) will be summarized for each treatment group.

18.1.7. NON TEAES

The non-TEAEs, the events occurred during the run-in phase before randomization, will be summarized separately. The frequency and percentage of patients experiencing non-TEAEs, serious non-TEAE, withdrawing during the run-in phase due to non-TEAE during run-in phase, Deaths before the active treatment start will be summarized. All enrolled patients who enter into the run-in period will be considered for this summary.

18.2. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol section 6.5.2.3.

Presentations will use SI Units as provided by the central laboratory Q2.

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.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements). Descriptive summaries will be presented for the actual and the changes from baseline at each visit. Changes from baseline will be analyzed using the same MMRM model then the primary efficacy variable, but without any imputation. LSMeans for each treatment group and associated SE/2-sided 95% CI will be presented. Differences in LSMeans will also be calculated with the SE, 2-sided 95% CI and p-value.

- Incidence of markedly abnormal laboratory criteria. The number of patients and percentages will be provided for each treatment group at each visit for each markedly abnormal criteria.

- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)

18.2.1. 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.

The markedly abnormal criteria are defined in the table below:

Laboratory Category	Parameter (unit)	Markedly Abnormal Low	Markedly Abnormal High
Hematology	WBC(X10E3 cells/µl)	<2.0	>20.0
	Neutrophil count (X10E3 cells/µl)	<1.0	NA
	Hemoglobin (g/dL)	<8.0	>20
	Platelets(cells/µl)	<50	>999
Biochemistry	ALT	NA	>3XULN
	AST	NA	>3XULN

Laboratory Category	Parameter (unit)	Markedly Abnormal Low	Markedly Abnormal High
	ALK phosphatase	NA	>3XULN
	Total Bilirubin	NA	>2XULN
	LDH (IU/L)	NA	>800
	Glucose (mg/dL)	<55	>270
	Creatinine	NA	>1.5XULN
	BUN (mg/dL)	NA	>60
	CPK(U/L)	NA	>850
	Sodium (mEq/L)	<130	>155
	Potassium(mEq/L)	<3.0	>6.0
	Total Protein(g/dL)	NA	>9.5
	Albumin(g/dL)	<2.0	NA
	Calcium (mg/dL)	<7.0	>12.5
	Lipase(U/L)	NA	>180
Lipids	Triglycerides (mg/dL)	<10	>900
	Total Cholesterol (mg/dL)	<20	>400
	LDL Cholesterol (mg/dL)	<20	>350
	HDL Cholesterol (mg/dL)	<20	NA

18.3. ECG EVALUATIONS

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

Frequency and percentage of overall assessment of ECG (investigator's judgment) will be presented i.e. the percentage of patients in categories such as normal, abnormal/not clinically significant and abnormal/clinically significant will be summarized. A Fisher's exact test will be performed between the treatment groups.

18.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

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

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit. Descriptive summaries will be presented for the actual and the changes from baseline at each visit. Changes from baseline will be analyzed using the same MMRM model than the primary efficacy variable, but without any imputation. LSMeans for each treatment group and associated SE/2-sided 95% CI will be derived. Differences in LSMeans will be calculated with the SE, 95% CI and p-value.
- Incidence of potentially clinically significant vital signs. The number of patients and percentages will be provided for each treatment group at each visit and overall visit (patient will be counted as clinically significant if at least one clinically significant occurred in all the visits. Fisher exact test will be performed between the treatment groups.
- Listing of patients meeting markedly abnormal criteria

18.4.1. POTENTIAL CLINICALLY SIGNIFICANT CHANGES

Potential clinically significant Vital Signs measurements will be identified in accordance with the

following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mm Hg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mm Hg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 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
Body temperature	℃	NA	≥ 38.3 ℃ AND change from baseline ≥ 1.1 ℃
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

18.5. PHYSICAL EXAMINATION

Physical examination will not be recorded in the CRF, any findings will appear in medical history or adverse events. The date of physical examination will be listed in a listing.

18.6. OTHER SAFETY ASSESSMENTS

18.6.1. IMMUNOGENICITY PROFILES ANALYSES

The following parameter will be summarized for immunogenicity:

1) Total Insulin Antibodies
   - Percent Binding (% B/T)
   - Positive/Negative
2) Cross Reactive Insulin Antibodies
   - Percent Binding (% B/T)
   - Positive/Negative

3) Insulin (Drug), Specific Antibodies

- Percent Binding (% B/T)

Descriptive statistics will be tabulated by treatment and by timepoint for the continuous variables. Change from baseline to post-baseline timepoints will also be presented. The same MMRM model as the primary efficacy analysis (without imputing missing data and excluding the basal insulin dosing time)) will be used. Estimates of the means, LSMeans (SE and 2-sided 95% CIs) as well as treatment difference at each visit will be presented. Analyses will be done on the Safety Population.

The dichotomous outcomes will be summarized with frequency and percentage at scheduled visits. Treatment comparison will be performed using Fisher's exact test. P-value for the two-sided test will be presented.

Potential immunogenicity effect on local and systematic allergic reaction, hypersensitivity, and severe hypoglycaemia will be explored by summarizing those incidences between the treatment groups among subjects with post-baseline positive response of cross reactive antibodies. The local and system allergic reactions as well as the hypoglycaemia are found directly on the CRF, the hypersensitivity events will be found in the coded adverse events with the following specifications:

- System Organ Class (SOC): Immune system disorders
- High Level Group Term (HLGT): Allergic conditions
- High Level Term (HLT): Allergies to foods, food additives, drugs and other
- Preferred Term (PT): Drug hypersensitivity
- Lower level term (LLT): Drug hypersensitivity

The possible insulin neutralization effect will also be explored by presenting:

- The incidence of patients with increase over 10% in cross reacting antibody from baseline at any visit
- The incidence of patients with increases of HbA1c over 0.2% increase from baseline at any visit
- The incidence of patients with increase in total or basal insulin dose at any visit.

Treatment group comparisons will be performed by using a Chi-Square test, if 80% of the cells have an expected frequency >=5 otherwise Fisher's exact test will be used.

18.6.2. 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, nocturnal hypoglycemia. Patients will be instructed to record all hypoglycemic events in the patient's 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.

The classification will be derived as follows:

- Severe: the patients entered in the eCRF: “severe (external assistance required to resolve event)”
- Documented Symptomatic Hypoglycemia: the patient entered in the eCRF: symptomatic and checked the “glucose value was less than or equal to 70 mg/dL”.
- Asymptomatic Hypoglycemia: the patient entered in the eCRF: asymptomatic (symptoms of hypoglycemia not present) and checked the “glucose value was less than or equal to 70 mg/dL”.
- Probable Symptomatic Hypoglycemia: the patient entered in the eCRF: symptomatic and checked the “glucose was not measured”.
- Relative Hypoglycemia: the patient entered in the eCRF: asymptomatic or symptomatic and checked the “glucose value was over 70 mg/dL”.
- Nocturnal Hypoglycemia: the patient has any of the 5 types above and also checked the “Nocturnal” time of the event.

Hypoglycemia event 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 event rate per patient per 30 days will be analyzed using the same MMRM model as for the primary efficacy parameter (without imputing any missing data).

For change from baseline of hypoglycemia rate, a graphical display at scheduled visits, of LSMeans and 2-sided 95% CI will be generated from the MMRM model. Additionally, mean (+/- SD) for actual measurements by visit will also be presented.

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.

19. STUDY DATA TECHNICAL CONFORMANCE

The data will be submitted using the Clinical Data Interchange Standards Consortium (CDISC). The Study Data Tabulation Model (SDTM) data will use version 1.4 (SDTMIG). The derived datasets will follow the Analysis Data Model (ADAM) and will use version 1.1 (ADAMIG).

20. DATA NOT SUMMARIZED OR PRESENTED

Not applicable.

21. REFERENCES

Yan, X., Lee, S., and Li, N. (2009), "Missing Data Handling Methods in Medical Device Clinical Trials," Journal of Biopharmaceutical Statistics, 19, 1085–1098. [392]

APPENDIX 1. REPORTING CONVENTIONS

Page Layout:

The Section 14 tables and Appendix 16 listings should be in landscape orientation by default.

The output in Section 14 and Appendix 16 will be in RTF file formal using Courier New font with 8 point size.

Statistical conventions:

The patient percentages (%) should be rounded to a whole number, with SAS rounding options used to obtain the values.

Percentages for values in the tables that are less than <1 should be presented as “<1”.

If “%” is part of the column heading, do not repeat the “%” sign in the body of the table.

If a value is zero (0), then do not use 0% and leave the corresponding percentage blank.

The format for range should always be “Min, Max”.

If there are missing data, then a missing row will be added to keep track of all patients. If there are no missing data, then delete the missing row. Percentages will not be presented on the missing category row.

Standard Deviation should be abbreviated as “SD”, and Standard Error should be abbreviated as “SE”; it is presented within parenthesis next to the mean value, without any +/- sign. The Standard Deviation or Standard Error should have one additional decimal point beyond that of the mean (for example, if the mean has one decimal point, SD/SE should have two decimal points). Mean and medican should have one additional decimal point beyond that of the data being summarized.

“N” will represent the entire treatment group, while “n” will represent a subset of the treatment group. For tables with population designated as a row heading, “N” should be used (i.e. tables where all the participant data is not available for every variable within a treatment group). As a guideline, if the number is used in denominator that it should be presented as “N”. If the number is used in numerator it should be presented as “n”.

P-values will be presented with 4 decimals.

APPENDIX 2. 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

START DATE	STOP DATE	ACTION
	Missing	Assumed TEAE
Missing	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

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

START DATE	STOP DATE	ACTION
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
	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 3. SAS CODE EXAMPLE FOR MULTIPLE IMPUTATION

```
/* First, generate enough data to produce a monotone missing data pattern */
/* MCMC does not work with class statement. Pooled investigator sites and */
/* baseline insulin dose time have been converted to indicator variables  */
/* For pooled investigator sites, let say that x is the total number of   */
/* pooled investigator sites.  Then, for pooled investigator sites #1,    */
/* inv01=1, inv02=0, …, inv0[x-1]=0                                       */
/* For pooled investigator sites #2, inv01=0, inv02=1, …, inv0[x-1]=0     */
/* For pooled investigator sites #[x-1], inv01=0, inv02=0, …, inv0[x-1]=1 */
/* For pooled investigator sites #x, inv01=0, inv02=0, …, inv0[x-1]=0     */
/* For baseline insulin dose time= morning, binstime=1                    */
/* For baseline insulin dose time= evening, binstime=0                    */
/* No rounding or range is applied for any variable                       */
/* Non-informative prior is proc mi default MCMC prior information        */
/* 200 is proc mi default number of burn-in iterations                    */
proc mi data = <<insert input dataset name>> out = datamono
        seed =20171220
        NIMPUTE=100;
   by trt;
   var inv01 inv02 … inv0[x-1] binstime HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
   mcmc impute = monotone chain= multiple;
run;


/* Then, do full imputation based on sequential regression models          */
/* assuming monotone missing pattern.                                      */
proc mi data = datamono seed = 171016 out = datami NIMPUTE = 1;
   by _imputation_;
   class inv01 inv02 … inv0[x-1] binstime trt;
   var inv01 inv02 … inv0[x-1] binstime trt HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
   monotone regression;
run;


/* Compute Changes from Baseline and create one categorical variables for  */
/* the pooled investigational sites based on the [x-1] indicator pooled    */
/* investigational site variables                                          */
data datmichg;
   set datami (in=a drop = HbA1c_WK18 rename = (HbAc1_WK12 = result))
       datami (in=b drop = HbA1c_WK12 rename = (HbAc1_WK18 = result));

   * Visit;
   if a then visit = "Week 12";
      else if b then visit = "Week 18";

   * Change from baseline;
   change = result - HbA1c_BASE;
```

```
   * Pooled investigational sites as 1 categorical variable;
   if inv01 = 1 then psites = 1;
      else if inv02 = 1 then psites = 2;
      …
      else if inv0[x-1] = 1 then psites = [x-1];
      else psites = x;
run;

/* MMRM Analysis by  imputation_ */
proc sort data=datmichg;
   by _imputation_ psites binstime trt visit subject;
run;

proc mixed data = datmichg method = REML;
   by _imputation_;
   class psites binstime trt visit subject;
   model change = HbA1c_BASE psites binstime trt visit trt*visit / DDFM = KR;
   random subject;
   repeated visit / type = UN subject = subject;
   lsmeans trt*visit /diff cl;
   ods output diff = lsdiffs(where=(trt= 'Process IV' and _trt='Process V' and
   visit=_visit));
run;

/* Combine LSmean Differences for Visit 'Week 12' */
proc mianalyze parms(classvar = full) = lsdiffs (where = (visit = 'Week 12'));
   class trt*visit;
   modeleffects trt*visit;
run;

/* Combine LSmean Differences for Visit 'Week 18' */
proc mianalyze parms(classvar = full) = lsdiffs (where = (visit = 'Week 18'));
   class trt*visit;
   modeleffects trt*visit;
run;
```

Note to programmers: In case of non-convergence or non-estimability issues for the generation of enough data to produce a monotone missing data pattern, replace the two proc mi by the following:

```
proc mi data = <<insert input dataset name>> out = datamono
        seed =20171220
        NIMPUTE=100
        round = 1 1 1 … 1 1 . min = 0 0 0 … 0 0 . max = 1 1 1 … 1 1 . ;
   var trt inv01 inv02 … inv0[x-1] binstime HbA1c BASE HbA1c_WK12 HbA1c_WK18;
   mcmc impute = monotone chain= multiple prior=ridge=p;
run;
```

```
proc mi data = datamono seed = 171016 out = datami NIMPUTE = 1;
   by _imputation_;
   class trt inv01 inv02 … inv0[x-1] binstime;
   var trt inv01 inv02 … inv0[x-1] binstime HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
   monotone regression;
run;
```

APPENDIX 4. SAS CODE EXAMPLE FOR TIPPING POINT

```
/*An MNAR version of the MI procedure from Appendix 3 will be used.
  The SHIFT value will start at 0.01 and be incremented until the critical
value for non-inferiority of 0.4 is surpassed.  In particular, the upper limit
of the 95% confidence interval of the treatment difference will be calculated
for each iteration of the 0.01 increase to the MNAR adjustment and once it
surpasses 0.4, we take that MNAR adjustment value as k.

Note: Code assumes TRT=1 is Process VI (Test) and TRT=2 is Process V
(Control).

The code for the MNAR MI proc which differs from the MAR MI proc in Appendix 3
is shown below.


proc mi data = <<insert input dataset name>> out = datamono
        seed =20171220
        NIMPUTE=100;
   by trt;
   MNAR     Adjust (<Week18VariablefromTranspose>/SHIFT= +Kprime
      ADJUSTOBS=(TRT='1'))
            Adjust (<Week18VariablefromTranspose>/SHIFT= -Kprime
      ADJUSTOBS=(TRT='2'));

   var inv01 inv02 … inv0[x-1] binstime HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
   mcmc impute = monotone chain= multiple;
run;
```

Where Kprime is the shift value starting at 0.01 and ending at k.

STATISTICAL ANALYSIS PLAN

MYL-1501D-3004

A RANDOMIZED, MULTI-CENTER, DOUBLE-BLIND, PARALLEL-GROUP CLINICAL STUDY COMPARING THE EFFICACY AND SAFETY OF MYL-1501D PRODUCED BY TWO MANUFACTURING PROCESSES IN TYPE 1 DIABETES MELLITUS PATIENTS.

AUTHOR: IRENE DEHEM

VERSION NUMBER AND DATE: V2.0 18OCT2018

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 18OCT2018) for Protocol MYL-1501D-3004 V2.

	Name	Signature	Date
Author:	Irene Dehem		18 OCT 2018
Position:	Statistical Scientist		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	Edith Simeon/Senior Reviewer		18-Oct-2018
Position:	Manager Biostatistics		
Company:	IQVIA		
Approved By:	Bin Sun		18-Oct-2018
Position:	Principal Biostatistician		
Company:	Mylan		

OUTPUT TEMPLATES SIGNATURE PAGE

Output Templates V2.0 (Dated 18OCT2018) for Protocol MYL-1501D-3004 V2.

	Name	Signature	Date
Author:	Irene Dehem		18OCT2018
Position:	Statistical Scientist		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Output Templates Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	Edith Simeon/Senior Reviewer		18-Oct-2018
Position:	Manager Biostatistics		
Company:	IQVIA		
Approved By:	Bin Sun		18-Oct-2018
Position:	Principal Biostatistician		
Company:	Mylan		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	04MAY2018	Irene Dehem	Not Applicable – First Version
2.0	16OCT2018	Irene Dehem	Adding footnote to Schedule of Events in section 4.2. Added visit windows in section 7.4 for mapping the unscheduled visit if scheduled visit is missing for HbA1c data. Updated site pooling information in section 8.2 to detail site pooling information. Added clarification for sensitivity analysis in section 16.1.2 and 16.1.4 to handle subjects who switch to their own insulin Lantus. Added clarification for immunogenicity data and PK analysis in sections 16.3 and 18.6.1 for excluding immunogenicity data and PK data from database lock. Added clarification on definition of baseline hypoglycemia period in section 18.6.2.

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
ATC	Anatomical Therapeutic Chemical (class)
BDR	blind data review
BMI	Body Mass Index
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference of Harmonization
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MAR	missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	mixed model for repeated measures
PP	Per Protocol
PT	Preferred Term
RND	randomized population
SAE	serious adverse event
SAF	Safety
SAP	statistical analysis plan
SE	standard error
SMBG	Self Monitored Blood Glucose
SOC	System Organ Class
TEAE	treatment emergent adverse event
T1DM	type 1 diabetes mellitus
WHO-DD	World Health Organization – Drug Dictionary (enhanced)

2. 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-3004. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol amendment 1 (dated 11JAN2018).

3. STUDY OBJECTIVES

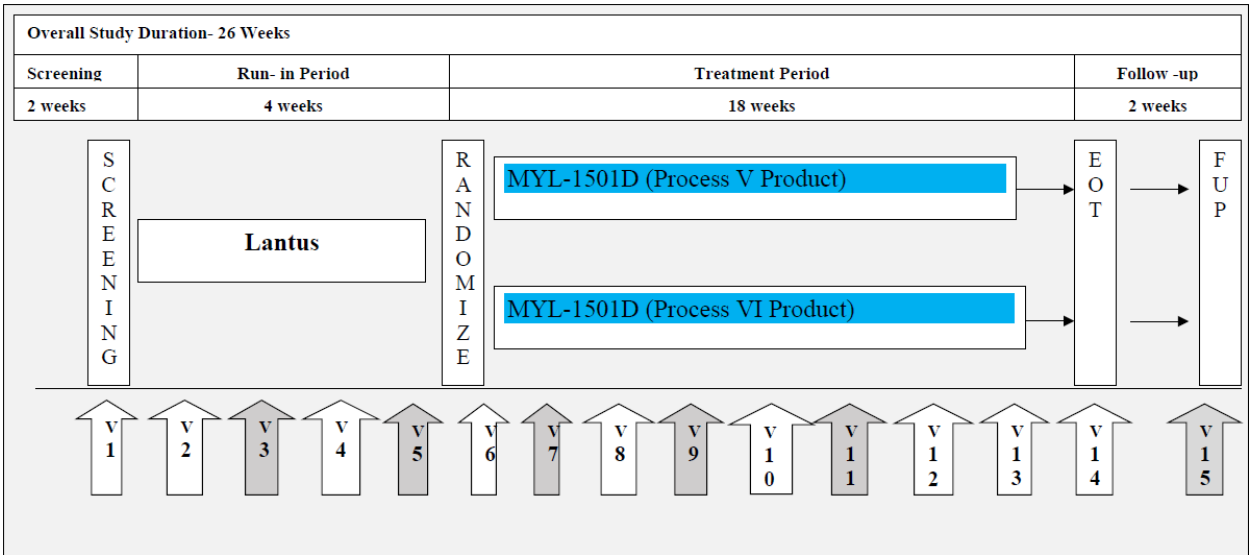
The primary objective is to test whether MYL-1501D product from Process VI once daily is non-inferior to MYL-1501D product from Process V once daily based on the change in HbA1c from baseline to week 18 when administered in combination with mealtime insulin lispro.

3.1. OTHER OBJECTIVES

The other objectives are to compare MYL-1501D product from Process VI and Process V at week 18, when administered in combination with mealtime insulin lispro, with respect to:

- Immunogenicity: incidence and change from baseline in the relative levels of anti-drug antibody
- Hypoglycemic events: incidence and rate per 30 days
- Occurrence of local reactions, systemic reactions and other adverse events
- Device-related safety assessment
- Change in fasting plasma glucose from baseline
- Change in insulin dose per unit body weight (U/kg) from baseline
- Change in 8-point Self-Monitored Blood Glucose (SMBG) profile from baseline

4. STUDY DESIGN



4.1. GENERAL DESCRIPTION

This is a multicenter, double-blind, randomized, parallel-group phase 3 study in patients with type 1 diabetes mellitus (T1DM) comparing the efficacy, immunogenicity and safety of MYL-1501D products from two manufacturing processes (Process V and Process VI). A total of 202 patients with T1DM are planned to be randomized in a 1:1 ratio between MYL-1501D Process V and MYL-1501D Process VI. Approximately 110 sites will be included in the study.

After up to 2-week screening period, all patients will be titrated on Lantus® during a 4-week run-in period, and will be shifted from their current mealtime insulin to Humalog®. The patients will be randomized (stratified by investigational site and time of administration of glargine [morning and evening]); one group will receive MYL-1501D product from Process V, while the other group will receive MYL-1501D product from Process VI for 18 weeks. A follow-up visit will be scheduled 2 weeks after last dose of MYL-1501D.

The none hypothesis is that the upper bound of treatment difference (Process VI minus Process V) is over 0.4 and alternative hypothesis is that upper bound of treatment difference is less than or equal to 0.4.

Patients will remain blinded until the database is locked, then an unblinding request form will be sent to the IVR provider in order to get the randomization code. Any analyses done prior to database lock will use dummy treatments.

4.2. SCHEDULE OF EVENTS

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									F-U
Study Visits[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT)	V15 (FU)
Study Week	-6 to -4	-4	-3	-2	-1	0	1	2	4	6	9	12	15	18	20
Study Days	-42 to -28	-28±3	-21±3	-14±3	-7±3	0±3	7±3	14±3	28±3	42±3	70±7	84±7	112±7	126±7	140±7
Informed Consent	x														
Inclusion/Exclusion Criteria Review	x					x									
History of previous insulin usage	x														
Dilated Ophthalmoscopy / retinal photography if not done in the last 6 months	x														
Standard-of-care specifics[2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Age, Gender, Height, Race	x														
Body Weight and BMI	x					x		x		x		x		x	
Pregnancy Test[3]	x					x		x		x		x	x	x	
Medical History including concomitant illness	x														
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vitals signs measurement (sitting)	x	x		x		x		x		x		x		x	
Physical examination	x					x								x	
12-lead ECG (supine)	x					x								x	
Randomization						x[8]									
Record AEs and SAEs (including local and systemic allergic reactions) and hypoglycemic events[4] due to medication, disposable pen or needle		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record device safety information			x	x	x	x	x	x	x	x	x	x	x	x	

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									F-U
Study Visits[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14 (EOT)	V15 (FU)
Study Week	-6 to -4	-4	-3	-2	-1	0	1	2	4	6	9	12	15	18	20
Study Days	-42 to -28	-28±3	-21±3	-14±3	-7±3	0±3	7±3	14±3	28±3	42±3	70±7	84±7	112±7	126±7	140±7
Fasting plasma glucose	x	x		x		x		x		x		x		x	
HbA1c Assay	x					x						x		x	
Fasting C-peptide, HIV, HBsAg, and HCVAb	x														
Sampling for hematology, blood chemistry and urinalysis[5]	x					x								x	
Fasting lipid profile	x					x						x		x	
Sampling for immunogenicity [9]	x					x		x		x		x		x	
Sampling for PK[6]						x		x		x		x		x	
Review 8-point SMBG Profile performed in the week before the visit [7]			x	x	x	x				x		x		x	
Dose review of Lantus, MYL-1501D and insulin lispro and instruction		x	x	x	x	x	x	x	x	x	x	x	x	x	
Dispense Study Medication and ancillary supplies		x				x				x		x			
Drug Accountability and Compliance				x		x		x		x		x	x	x	
Dispense subject diary		x				x				x		x			
Review subject diary				x		x				x		x		x	

1. Visits 3, 5, 7, 9 and 11 may be telephone contacts *(*grey columns represent telephone contacts).
2. Standard–of-care specifics includes assessment and documentation of the following - Training on self-management of diabetes, lifestyle modification measures (includes maintenance of appropriate body weight, following recommended physical activity, avoidance of smoking and following the recommended diet); and monitoring to prevent complications.
3. Serum pregnancy test for women of child bearing potential will be done during screening and randomization visit. During subsequent visits urine pregnancy test will be done. At the randomization visit, both urine and serum pregnancy tests will be done. Subject may be enrolled if the urine pregnancy test is negative.
4. Non-severe hypoglycemic events (which are not consider as SAE) occurring after the EOT visit will not be recorded at the follow-up visit.
5. A routine urine dipstick test will be performed by the site. A microscopic urinalysis will be performed by the central lab if the dipstick test result is abnormal.
6. The PK sample will be taken during the visit, preferably prior to the daily glargine dose. The timing of study drug administration from prior day should be collected along with the time of PK sample collection.

7. The 8-point SMBG profile, measurement will be done by the subject at home on 3 days (of which 2 are consecutive days) in the week before the next visit. Evaluation will be based on the measurements after each 6 weeks; thus during randomized period it would done at Week 6, 12 and 18, while SMBG would be done on 3 days during Weeks 5, 11 and 17.
8. Prior to randomization, Investigator is required to confirm subject eligibility into the study based on the data collected during the screening period, including the labs values recorded during screening. In case subject does not meet the eligibility re-screening need to be confirmed by the Sponsor or designee.
9. During the Randomized Comparative Treatment Period, the immunogenicity samples should be drawn immediately following the PK sample, as outlined under Footnote 6.

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

No changes.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

5.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC or interim analysis for this study.

5.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this SAP, Sponsor Authorization of Analysis Sets, Database Lock and Unblinding of Treatment.

6. ANALYSIS SETS

Agreement and authorization of patients included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

6.1. ALL PATIENTS SCREENED

The all patients screened population is defined as all patients who consent for the study.

6.2. RUN-IN POPULATION

The run-in population is defined as all patients who consent for the study and entered into the run-in phase. The patients in this population will be summarized under the total number of patients. Run-in failure patients will be summarized under the category of "run-in failure".

6.3. ALL PATIENTS RANDOMIZED POPULATION [RND]

The all patient randomized (RND) population will contain all patients got randomized to study medication. The patients who discontinue the study during run-in period will not be included in the randomized population.

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

6.4. INTENT-TO-TREAT POPULATION [ITT]

The Intent-to-Treat (ITT) population includes all randomized patients (including patients who receive incorrect treatment, do not complete the trial or do not comply with the protocol).

The patients under the ITT population will be analyzed according to the planned treatment group.

All primary and secondary efficacy analysis will be based on the ITT population.

6.5. SAFETY POPULATION [SAF]

The safety population (SAF) will contain all patients who are randomized and take at least one dose of study drug.

The safety analysis will be conducted according to the treatment received. If there is any doubt whether a patient was treated or not, they will be assumed treated for the purpose of the analysis.

6.6. PER PROTOCOL POPULATION [PP]

The per-protocol population (PP) will contain all patients who complete week 18 and have HbA1c3 measurements as per the protocol, or have at least one post-baseline HbA1c data for patients who discontinue prematurely, and do not have major protocol deviation that impact the primary outcome. Patients who meet rescue medication criteria and take rescue medication will be excluded from the PP. The list of deviations leading to exclusion from the PP population will be identified, reviewed and documented prior to DB lock and determined in the blind data review meeting and documented in the blind data review report prior to the database lock. The subjects who are excluded from PP population and reason for exclusion will be listed.

7. GENERAL CONSIDERATIONS

7.1. 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 randomization, (Day 1 is the day of randomization).

- 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.

7.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to receiving randomized treatment reference (day of randomization) start date (including unscheduled assessments). In the case where the last non-missing measurement and the randomized treatment start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the randomized treatment start date will be considered post-baseline.

For insulin (mealtime, basal and total) levels, baseline is the value collected at Visit 6 (Week 0) which correspond to values collected prior injection of study medication.

7.3. 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 scheduled visit if scheduled visit value is missing or the Last Observation Carried Forward (LOCF) value in case primary sensitivity analysis, or best/ worst case value where required (e.g. shift table) in safety analysis.

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 entered under the Visit 14 (week 18), but for summary tables it will be

mapped to the next available planned visit number after their last scheduled visit. For example, should a patient discontinue at Visit 9, the Early Termination visit will have their Fasting plasma glucose and their HbA1c assay taken. The fasting plasma glucose would then be summarized under Visit 10 and the HbA1c under Visit 12.

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

7.4. WINDOWING CONVENTIONS

Visit windowing will be performed only on HbA1c data. Should a visit have a missing value, the unscheduled visit will be used and mapped by using the following algorithm.

Days to first dose of unscheduled measurement	Mapped Visit
-42 to -28 days	Visit 1 (Week -6 to -4)
-27 to -25 days	Visit 2 (Week -4)
-24 to -18 days	Visit 3 (Week -3)
-17 to -11 days	Visit 4 (Week -2)
-10 to -4 days	Visit 5 (Week -1)
-3 to 3 days	Visit 6 (Week 0)
4 to 10 days	Visit 7 (Week 1)
11 to 17 days	Visit 8 (Week 2)
25 to 31 days	Visit 9 (Week 4)
39 to 45 days	Visit 10 (Week 6)
63 to 75 days	Visit 11 (Week 9)
76 to 91 days	Visit 12 (Week 12)
105 to 119 days	Visit 13 (Week 15)
121 to 133 days	Visit 14 (Week 18)
134 to 147 days	Visit 15 (Week 20)

For subjects who discontinue the study, their early termination HbA1c value will be remapped to their actual visit using the same time window as desctibed above.

7.5. STATISTICAL TESTS

The default significant level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

Non-inferiority will be tested at 2.5% (one-sided) level of significance.

7.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

7.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

8. STATISTICAL CONSIDERATIONS

8.1. 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.

- Pooled sites
- Time of Glargine administration (morning, evening), stratification factor.
- Baseline HbA1c (continuous variable)

8.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers in the USA.

When specified, statistical analysis will be adjusted for pooled sites based on US census regions.

All sites are grouped by state.

All states within a US census region (Northeast, Midwest, South, West, Pacific) with fewer than 8 randomized patients will be combined into a single pooled site for analysis purposes. The maximum number of subjects can not exceed 40 per site.

The pooled method will be as follow (performed manually):

Sites within a census region (New England, Midwest, South, West) with less than 8 randomized patients will be pooled with the closest' sites within the same census region until they reach at least 8 subjects.

Pooled Site Group	Site ID (number of subjects per site)	Total Number of Subjects
Pool_1 (Midwest_1)	40016 (2), 40029 (2), 40038 (1), 40059 (2), 40074 (1), 40097 (2), 40098 (2), 40100 (1)	13
Pool_2 (Midwest_2)	40083 (3), 40086 (1), 40095 (5)	9
Pool_3 (North_1)	40040 (3), 40051 (2), 40062 (2), 40087 (3), 40096 (2), 40103 (1)	13
Pool_4 (South_1)	40009 (2), 40019 (1), 40026 (1), 40027 (1), 40035 (3), 40048 (4), 40057 (3), 40077 (4)	19
Pool_5 (South_2)	40012 (5), 40024(1), 40050 (4), 40078 (6)	16
Pool_6 (South_3)	40047 (4), 40075 (2), 40084 (1), 40106 (2)	9
Pool_7 (South_4)	40018 (2), 40030 (3), 40042 (1), 40054 (3), 40107 (1)	10
Pool_8 (South_5)	40025 (2), 40036 (3), 40037 (4), 40056 (2), 40108 (1)	12
Pool_9 (South_6)	40001 (4), 40004 (8), 40017 (3), 40033 (2), 40045 (3), 40046 (4), 40070 (3), 40088 (1), 40111(1)	29
Pool_10 (West_1)	40003 (3), 40005 (2), 40008 (6), 40014 (2), 40022 (1), 40049 (2), 40060 (3), 40061 (2), 40064 (2), 40071 (6), 40081 (3), 40082 (2), 40090 (3)	37
Pool_11 (West_2)	40021 (3), 40043 (2), 40079 (2), 40091 (6)	13
Pool_12 (West_3)	40020 (5), 40053 (3)	8
Pool_13 (West_4)	40011 (13), 40015 (6), 40092 (4)	23
Pool_14 (West_5)	40089 (4), 40093 (4)	8

8.3. MISSING DATA

After having mapped data captured at unscheduled and/or early termination visits (if any) to schedule missing visits using visit windows technique (refer to section 7.4), missing primary data will be imputed by using the multiple imputation (MI) technique (see section 16.1.3).

As another sensitivity analysis, the imputed values by MI will be corrected such that the full non-inferiority margin will be added for imputed values in Process VI group.

A sensitivity analysis using Last Observation Carried Forward (LOCF) will also be performed on the primary efficacy parameter.

In the secondary efficacy data, the weight used in the daily total insulin will be imputed by the weight of the previous visit value if current weight value is missing.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustment for multiplicity will be performed.

8.5. ACTIVE-CONTROL STUDIES INTENDED TO SHOW NON-INFERIORITY OR EQUIVALENCE

Non-inferiority will be established if the upper bound of a two-sided 95% confidence interval (CI) for the absolute difference (MYL-1501D Process VI minus Process V) of mean change from baseline to week 18 for HbA1c is less than or equal 0.4%.

8.6. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the exploratory analysis sections. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.

The following subgroups will be assessed and described within the subgroup analysis sections (16.2.4). A minimum of 8 subjects/arm in each subgroup is needed. For subgroup with less than 8 subjects/arm, this subgroup will be pooled with the other ones having less than 8 subjects/arm together and the subgroup will be named “other” if there are other subgroups with less than 8 subjects/arm exist.

- Gender:
  - Female
  - Male
- Age (years):
  - ≤ 21
  - > 21 to <65
  - ≥65
- Race in 5 categories:
  - American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or Other Pacific Islander
  - White
- Ethnicity in 2 categories:

- o Hispanic or Latino
- o Not Hispanic or Latino
- o Not reported or Unknown

9. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

10. 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 week 18 or discontinued early as well as completed the trial will be summarized for each treatment group. Reason for discontinuation during week 18 will be summarized. The summary of reason for discontinuation from the study will also be presented.

The number and proportion of patients withdrawing the study during the run-in phase will be presented. The number and proportion of patients in each population will also be summarized.

A listing of patients who fail the inclusion/exclusion criteria will be produced.

A summary of major protocol deviations will be provided as frequency and percentages. Protocol deviations in the run-in phase will be summarized separately. A list of all major protocol deviations will also be provided.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the RND and SAF populations.

The continuous demographic/baseline variables will be summarized using the mean, median, standard deviation, minimum, and maximum values. For categorical (nominal) variables, the number and percentage of patients will be used. No statistical testing will be carried out for demographic or other baseline characteristics. All demographic and baseline characteristics will be presented in a listing.

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

- Age (years) - calculated relative to date of informed consent
- Gender
- Race

- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Duration of diabetes (years)
- Time of glargine administration (morning, evening)
- Baseline fasting plasma glucose (mmol/L)
- Baseline HbA1c (%)
- Insulin use prior to screening (yes, no)
- Fasting C-Peptide, HIV, HBsAg and HCVAb (positive, negative)

11.1. DERIVATIONS

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

12. MEDICAL HISTORY

Medical History information will be presented for the SAF and coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 20. Coded medical history terms will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group. Multiple entries for an individual patient under same SOC/PT will only be counted once.

13. MEDICATIONS

Medications will be presented for the SAF and coded using WHO Drug dictionary 01SEP2017.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the reference start date.

- Insulin use prior first dose are any insulin medication used prior to screening visit.
- 'Concomitant' medications are medications which:
  - started prior to, on or after the randomization date
  - AND ended on or after the randomization date of study medication or were ongoing at the end of the study.

Prior and concomitant medication will be summarized by treatment group. The number of patients taking each medication will be presented by Anatomical Therapeutic Chemical (ATC) names (levels 1, 2, 3). Each patient taking the same therapy more than once will be counted once within each ATC code level. All prior and concomitant medications will be presented in data listing. A separate listing on prohibited medications will also be provided.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for the SAF.

The exposure will be summarized for each treatment group using the mean, standard deviation, median, minimum and maximum. Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

14.1. DERIVATIONS

Duration of exposure days = date of last study medication administration minus the date of reference day + 1.

Where the reference start date is defined in section 6.1 and the date of last study medication will be taken from the "End of Treatment" form.

15. STUDY TREATMENT NON-COMPLIANCE

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

- Missing total meal time insulin daily since last visit
- Missing basal insulin daily since last visit
- Took two times more basal insulin daily since last visit
- Took less or more than prescribed basal insulin dose units daily since last visit

Number and proportion of patients with non-compliance will be summarized along with individual categories of non-compliance for each category.

The non compliance proportion is defined as total accumulative non-compliant days/duration of treatment exposure in days. Summary of non-compliance proportion will be performed by each non-

compliance category for each treatment group. The treatment groups will be compared by using an ANOVA model which will include treatment and pooled-site.

16. EFFICACY OUTCOMES

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY VARIABLE

The primary efficacy variable is change in HbA1c from baseline to week 18 for the ITT population.

The HbA1c is analyzed by central laboratory Q2Solutions.

16.1.2. MISSING DATA METHOD AND DATA OBSERVED UNDER RESCUE MEDICATION FOR PRIMARY EFFICACY VARIABLE

After having mapped data captured at unscheduled and/or early termination visits (if any) to schedule missing visits using visit windows technique (refer to section 7.4), MI will be used for the primary efficacy analysis. Refer to section 16.1.3 for more details.

If subjects initiate rescue medication after Week 12, HbA1c value at Week 18 or subjects who switch to their own insulin Lantus, will be considered as missing and imputed as described above i.e., first remapped data collected at unscheduled/early termination visits (if any) to Week 18 and then, use MI to impute remaining Week 18 data.

16.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

Descriptive statistics will be tabulated by treatment and by time point of the actual HbA1c value and the changes from baseline.

The primary objective of this study is to test the hypothesis that MYL-1501D product from Process VI is non-inferior to MYL-1501D product from Process V based on change in HbA1c from baseline to week 18.

The primary efficacy analysis will be performed for the ITT analysis set.

Mean changes from baseline in HbA1c will be analyzed based on all observed data of schedule visits as well as data imputed using the unscheduled/early termination data (if collected) or MI methodology for schedule visits at which no value is captured (refer to section 16.1.2).

MI will be performed under the assumption of missing-at-random (MAR) and will be implemented in two steps.

First, partial imputation assuming MAR will be carried out to impute intermittent (non-monotone) missing data based on multivariate joint Gaussian imputation model using the Markov chain Monte

Carlo (MCMC) method. A separate model will be used for each treatment group. The imputation model will include the pooled investigator sites and basal insulin dose time (morning vs. evening) as fixed covariate and observed HbA1c values at baseline (visit 6), week 12 (visit 12) and week 18 (visit 14). The MCMC method in the MI procedure in SAS will be used with multiple chains, 200 burn-in iterations, and a non-informative prior. In case of non-convergence or non-estimability issues, a ridge prior and single model will be considered with treatment group added as explanatory variable to model.

Then, the remaining monotone missing data will be imputed using sequential regression multiple imputation, where a separate regression model is estimated for imputation of each variable (i.e., measurement at each visit) one after the other including the observed values and the values just imputed from the previous visit. Each regression model will include explanatory variables for pooled investigational sites, basal insulin dose time (morning vs. evening), treatment group and all previous (baseline (visit 6), week 12 (visit 12) and week 18 (visit 14)) values of HbA1c.

No rounding or range restrictions will be applied.

Imputed data will consist of 100 imputed datasets. The random seed number for the partial imputation with the MCMC method will be 20171220, and the random seed number for the sequential regression MI will be 171016.

Each of the 100 imputed datasets will be analyzed using the following analysis method. Change from baseline in HbA1c to each post-baseline visit will be calculated based on observed and imputed data. Mean changes from baseline in HbA1c values will be analyzed using a mixed model for repeated measures (MMRM) approach. Restricted maximum likelihood (ReML) estimation will be used. The MMRM model will include the changes from baseline in HbA1c values as dependent variables, the baseline HbA1c values as fixed covariate, pooled investigational sites, basal insulin dose time (morning vs evening), treatment group (MYL 1501D Process V and MYL 1501D Process VI), visit (week 12 and week 18), and treatment group by visit interaction as fixed effects, and subjects as random effect. An unstructured covariance structure will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. If this analysis fails to converge, the following covariance structures will be tested: AR(1), ARH(1), CS, CSH, TOEP, TOEPH. The covariance structure converging to the best fit, as determined by Akaike's information criteria (AIC) will be used as the primary analysis.

Treatment group comparison at week 18 will be based on the least square mean (LS mean) difference between treatment groups (i.e., MYL 1501D Process VI – MYL 1501D Process V) in change from baseline in HbA1c estimated by the model in each imputed datasets. Results from analysis of each imputed dataset i.e., LS mean differences and their standard error (SE), will be combined using the Rubin's imputation rules to produced pooled LS mean estimate of treatment difference and its 2-sided 95% confidence interval (CI).

Non-inferiority will be established if the upper limit of the two sided 95%CI for the difference (MYL-1501D Process VI minus Process V) of mean change from baseline to endpoint for HbA1c is not greater than 0.4% at week 18.

Refer to APPENDIX 3 for SAS code example.

For graphical display at scheduled visits, the LS Means and 2-sided 95% CI for the changes from baseline in HbA1c to week 12 and week 18 obtained from the MMRM model will be presented by treatment group. Similar graphical display will be presented for the mean actual HbA1c values and SD over time by treatment group.

16.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

- Sensitivity to analysis set: the PP population will be used with the same MMRM model described above to establish non-inferiority. For sensitivity analysis, all non-missing HbA1c data will be used regardless if subject switched their assigned study medication.
- Sensitivity to missing data assumptions:
  - Same analysis approach as the primary analysis, but without imputing missing values. This will be analyzed based in ITT.
  - In another method, the same analysis approach as the primary analysis will be performed, but the imputed values will be corrected such that the full non-inferiority margin will be added for imputed values in Process VI group. This will be analysed based on ITT.
  - In a third sensitivity analysis, tipping-point analysis will be performed using an algorithm proposed by Yan et al (2009) to explore the robustness of the results with regard to a bias against the Process VI treatment arm and in favour of the Process V treatment arm. In order to quantify the bias (k), scenario 2 of the Yan et al (2009) algorithm will be used. Missing Week 18 values will have the value k (positive) added to the Process VI arm (worsening results) and subtracted from the Process V arm (improving results). The value for k is determined by adjusting the bias in an MNAR version of starting with a value of 0.01 and increasing it until the MNAR version of the MI method described in Appendix 4 meets or surpasses the non-inferiority margin. That is the upper limit of 95% interval of treatment difference is > =0.4 (p-value for test non-interiority is >=0.05). The seed and code for this process are detailed in Appendix 4. The shift parameter as well as summary statistics for the MI model with the tipping point adjustment of k will be reported.
  - As a final sensitivity analysis, missing data will be imputed by using LOCF. An ANCOVA model will be used on the change from baseline in HbA1c to month 18. The model will include treatment (2 levels: MYL-1501D Process V and MYL-1501D Process VI) as fixed effect, the baseline HbA1c as covariate, and patient as random effect. The pooled sites and basal insulin dose time (morning or event) will also be included in the model as fixed effects. This will be analyzed on ITT and PP.
  - In addition, the means for each treatment and difference between treatments for missing data at Week 18 will be summarized for all sensitivity analyses.

16.2. SECONDARY EFFICACY

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

16.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.2.1.1. Fasting plasma glucose

The fasting plasma glucose is collected at baseline, week 2 (visit 8), week 6 (visit 10), week 12 (visit

12) and week 18 (visit 14, End of Treatment). The measurements are performed by the central laboratory Q2.

Actual values and changes from baseline at each time point will be computed and summarized by treatment group.

A separate analysis will be performed excluding patients with no fasting status.

16.2.1.2. Daily insulin dose per unit body weight (mealtime, basal insulin and total) for days of 8-point profiles

Patients will be asked to document the dose of insulin taken on the same day they will perform the 8-point SMBG profiles (from week -3 to week 18). The measurements are taken the week prior to the visits, so the week prior to:

- Week -3 (Visit 3)
- Week -2 (Visit 4)
- Week -1 (Visit 5)
- Week 0 (Visit 6)
- Week 6 (Visit 10)
- Week 12 (Visit 12)
- Week 18 (Visit 14)

Doses will be recorded in the patient's 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 doses variables: meal time insulin dose, basal insulin and total insulin dose.

Daily Meal time insulin dose: is the sum of all the total daily meal time insulin (Humalog) dose over the double-blind treatment period divided by the number of days measured. For the computation of total daily mealtime doses, only the patients with at least three mealtime doses at a particular day are considered. That is, total daily mealtime dose will not be computed for a day if the mealtime dose is recorded less than 3 times for that day.

Daily Basal insulin dose: is the average of the insulin dose over days measured during the double-blind period.

Daily Total insulin: is the sum of all total daily meal time doses and all basal insulin doses over the double-blind treatment period divided by the number of days measured. Similarly to total daily mealtime dose for which less than 3 mealtime doses are recorded, the missing insulin doses will not be considered for the average computation. That is, if either the mealtime doses are recorded less than 3 times or the basal insulin dose is missing for a particular day of collection, total insulin dose will not be computed. The total insulin dose will be computed for the remaining days where basal insulin dose and at least 3 mealtime doses are collected.

All doses will be divided by total body weight (kg) to convert to daily insulin dose (U) per unit body weight (kg). If body weight at that visit is missing, the weight from previous visit will be used.

16.2.1.3. 8-point Self-Monitored Blood Glucose (SMBG) profile

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 3 days, 2 should be consecutive). The patient should document the 3 pre-visit measurements in the diary.

The following summaries will be summarized at week 6, 12, and week 18:

Individual 8-points SMBG:

The over 3 day averages will be performed for the measures taken at:

- Before breakfast
- Two hours after breakfast
- Before lunch
- Two hours after lunch
- Before dinner
- Two hours after dinner
- Just before sleep
- At 3:00 AM

Averages will be performed at each visit.

Excursions and averages in SMBG:

The following averages will be computed:

- Morning excursion
- Noon excursion
- Evening excursion
- Overall excursion
- Pre-meal average
- Post-meal average
- (4-point average) pre-meal and bedtime average
- Overall average

The 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 the overall excursion at morning, afternoon and evening, the individual excursion values obtained on each day will be averaged across the three days.

To compute the overall excursion, first the average of the morning, noon and evening excursion within a day will be computed, then the average will be done across the 3 days.

The pre-meal average will be the average of the following timepoints: before breakfast, before lunch, before dinner on each day, then the average will be done over the 3 days.

The post-meal average will be the average of the following timepoints: two hours after breakfast, two hours after lunch, two hours after dinner on each day, then the average will be done over the 3 days.

The pre-meal and bedtime average will be the average of the following timepoints: before breakfast, before lunch, before dinner, just before sleep, then the average will be done over the 3 days.

The overall average will be the average of all the 8 timepoints during a day. The daily average will not be computed for a day if more than 3 timepoints are missing on a particular day. The overall average will be kept missing if the daily average is missing for all three days. If the average is missing for one or two days, the average of the remaining days will be considered for the computation.

16.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

Imputation will be performed for the SMBG and weight for dose calculation as described in section 16.2.1.

16.2.3. Analysis of Secondary Efficacy Variables

16.2.3.1. Analysis of change from baseline in HbA1c at scheduled visits

Descriptive statistics will be presented for actual and change from baseline to scheduled visits for HbA1c.

Treatment group comparison will be done using the MMRM model as used for the primary endpoint (without imputing the missing values), including treatment, visit, treatment-by-visit interaction, pooled-investigator, basal insulin dosing time, as fixed effects, baseline values as covariate and subjects as random effect.

LSMeans for each treatment group, as well as associated SE and 2-sided 95% CI will be provided by visit. Differences in LSMeans will be calculated and associated 2-sided 95% confidence intervals and p-values will be provided for each visit.

16.2.3.2. Analysis of change from baseline in fasting plasma glucose

Descriptive statistics will be presented for actual and change from baseline to scheduled visits for fasting plasma glucose. A separate analysis will be done with excluding data with non-fasting status.

Treatment group comparison will be done using the MMRM model as used for the primary endpoint (without imputing missing values), including treatment, visit, treatment-by-visit interaction, pooled-site, basal insulin dosing time, as fixed effects, baseline values as covariate and subjects as random effect.

LSMeans for each treatment group, as well as associated SE and 2-sided 95% CI will be provided by visit. Differences in LSMeans will be calculated and associated 2-sided 95% confidence intervals and p-values will be provided for each visit.

For graphical display at scheduled visits the mean and SD plot will be prepared for the actual plasma

glucose measurement by visit and treatment group; LSMeans and 2-sided 95% CI from the same MMRM model will similarly be displayed graphically.

16.2.3.3. Analysis of Change in Daily insulin dose per unit body weight (mealtime, basal insulin and total) for days of 8-point profiles.

Descriptive statistics will be tabulated by treatment and by timepoint. Change from baseline to post-baseline timepoints will also be presented for insulin dose including daily basal insulin dose, daily meal time insulin dose, and daily total insulin dose.

These secondary efficacy parameters will be analyzed using the same MMRM model as the primary efficacy analysis (without imputing missing values). Estimates of the means, LSMeans (2-sided 95% CIs) as well as treatment difference at each visit will be presented.

A graphical display at scheduled visits with the mean and SD plot will be prepared for each of these secondary efficacy endpoints by visit and treatment group; LSMeans and 2-sided 95% CI from the same MMRM model will similarly be displayed graphically.

16.2.3.4. 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).

Descriptive statistics will be presented for the actual and change from baseline to scheduled visits for SMBG profile.

Treatment group comparison will be done using the same MMRM model as the primary efficacy analysis (without imputing missing values). Estimates of the means, LSMeans (2-sided 95% CIs) as well as treatment difference at each visit will be presented.

For graphical display at scheduled visits the mean and SD plot will be prepared for the actual Overall SMBG average measurement by visit, LSMeans and 95% CI from the same MMRM model will similarly be displayed graphically.

16.2.4. SUBGROUP ANALYSIS

The effect of subgroups mentioned in section 8.6 on the change from baseline HbA1c at week 18 will be examined by employing a MMRM model. The subgroups will be included in the model along with the treatment group. Additionally separate subgroup analysis within each subgroup mentioned in section 8.6 will be performed same MMRM model for treatment comparison within each subgroups.

The similar subgroups will also be examined for the immunogenicity parameters for the percent binding and the incidence analysis of cross reactive antibody. Besides examine subgroup by treatment interaction for percent binding. Separate analysis for both percent binding and incidence will be performed for treatment comparison within each subgroup.

16.3. EXPLORATORY PK ANALYSIS

Exploratory PK analysis will be performed by Mylan PK/DM department.

Descriptive statistics of PK concentration values will be presented for each scheduled visits by treatment group.

Treatment group comparison will be done using the GLM model on log-transformed PK concentration values including treatment, visit, treatment-by-visit interaction, time of administration of glargine [morning and evening], all as fixed effects. If treatment-by-visit interaction is not significant, this term will be dropped from the model, the reduced model will be performed to produce the final analysis. If treatment-by-visit interaction is significant, then this interaction term and visit term will be drop from the model and final model will be performed by visit with only treatment and time of administration in the model.

LSMeans for each treatment group and Geometric Mean Ratio between the treatment groups will be calculated. 2-sided 90% confidence intervals for the log transformed treatment difference and p-values will be provided.

The PK data will not be available at the time of database lock for the analysis. However the treatment will remain blinded during the laboratory assay. These data will be locked later and statistical analysis will be performed according to pre-specified method in this SAP

17. QUALITY OF LIFE ANALYSIS

Not applicable.

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set. Percentages will be computed on the total number of subjects in each treatment group.

18.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA central coding dictionary, Version 20.1.

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.

Events occurring in patients treated with the active comparator are also considered AEs.

An AE will be defined as treatment emergent (TEAE) if the first onset (or worsening in the case of pre-existing disease) is after randomization through follow-up visit or 14 days after last dose [for patients that do not have a follow-up visit].

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 within each of the categories described in the sub-sections below, will be provided as specified in the templates.

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

Listings will include TEAEs and Non-TEAEs.

18.1.1. ALL TEAEs

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

18.1.1.1. Severity

Severity is classed as mild/ moderate/ severe/ life-threatening/ death (increasing severity). TEAEs starting on or after the first dose of study medication with a missing severity will be classified as severe. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

18.1.1.2. Adverse Drug Reaction (Relationship to Study Medication)

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 reaction will be presented by treatment,

SOC and PT.

18.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the Treatment withdrawn field in the CRF under “Action taken with study medication”.

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

18.1.3. 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.

18.1.4. 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.

18.1.5. Local or Systemic Allergic Reaction

The local and systemic allergic reactions are recorded on the adverse events page of the eCRF.

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

18.1.6. Device-related Assessment

The relationship to the insulin glargine pen/needle and to the Humalog pen/needle are recorded on the adverse events page of the eCRF.

TEAE incidence will be summarized by SOC and treatment group for the insulin glargine pen/needle relationship and for the humalog pen/needle relationship and for both.

The incidence of device problems (even if not leading to an AE) will be summarized for each treatment group.

18.1.7. Non TEAEs

The non-TEAEs, the events occurred during the run-in phase before randomization, will be summarized separately. The frequency and percentage of patients experiencing non-TEAEs, serious non-TEAE, withdrawing during the run-in phase due to non-TEAE during run-in phase,

Deaths before the active treatment start will be summarized. All enrolled patients who enter into the run-in period will be considered for this summary.

18.2. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry and Urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol section 6.5.2.3.

Presentations will use SI Units as provided by the central laboratory Q2.

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.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements). Descriptive summaries will be presented for the actual and the changes from baseline at each visit. Changes from baseline will be analyzed using the same MMRM model then the primary efficacy variable, but without any imputation. LSMeans for each treatment group and associated SE/2-sided 95% CI will be presented. Differences in LSMeans will also be calculated with the SE, 2-sided 95% CI and p-value.

- Incidence of markedly abnormal laboratory criteria. The number of patients and percentages will be provided for each treatment group at each visit for each markedly abnormal criteria.

- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)

18.2.1. 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.

The markedly abnormal criteria are defined in the table below:

Laboratory Category	Parameter (unit)	Markedly Abnormal Low	Markedly Abnormal High
Hematology	WBC(X10E3 cells/µl)	<2.0	>20.0
	Neutrophil count (X10E3 cells/µl)	<1.0	NA
	Hemoglobin (g/dL)	<8.0	>20
	Platelets(cells/µl)	<50	>999
Biochemistry	ALT	NA	>3XULN
	AST	NA	>3XULN
	ALK phosphatase	NA	>3XULN
	Total Bilirubin	NA	>2XULN
	LDH (IU/L)	NA	>800
	Glucose (mg/dL)	<55	>270
	Creatinine	NA	>1.5XULN
	BUN (mg/dL)	NA	>60
	CPK(U/L)	NA	>850
	Sodium (mEq/L)	<130	>155
	Potassium(mEq/L)	<3.0	>6.0
	Total Protein(g/dL)	NA	>9.5

Laboratory Category	Parameter (unit)	Markedly Abnormal Low	Markedly Abnormal High
	Albumin(g/dL)	<2.0	NA
	Calcium (mg/dL)	<7.0	>12.5
	Lipase(U/L)	NA	>180
Lipids	Triglycerides (mg/dL)	<10	>900
	Total Cholesterol (mg/dL)	<20	>400
	LDL Cholesterol (mg/dL)	<20	>350
	HDL Cholesterol (mg/dL)	<20	NA

18.3. ECG EVALUATIONS

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

Frequency and percentage of overall assessment of ECG (investigator's judgment) will be presented i.e. the percentage of patients in categories such as normal, abnormal/not clinically significant and abnormal/clinically significant will be summarized. A Fisher's exact test will be performed between the treatment groups.

18.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

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

- Weight (kg)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit. Descriptive summaries will be presented for the actual and the changes from baseline at each visit. Changes from baseline will be analyzed using the same MMRM model than the primary efficacy variable, but without any imputation. LSMeans for each treatment group and associated SE/2-sided 95% CI will be derived. Differences in LSMeans will be calculated with the SE, 95% CI and p-value.

- Incidence of potentially clinically significant vital signs. The number of patients and percentages will be provided for each treatment group at each visit and overall visit (patient will be counted as clinically significant if at least one clinically significant occurred in all the visits. Fisher exact test will be performed between the treatment groups.

- Listing of patients meeting markedly abnormal criteria

18.4.1. POTENTIAL CLINICALLY SIGNIFICANT CHANGES

Potential clinically significant Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mm Hg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mm Hg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 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
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 %

18.5. PHYSICAL EXAMINATION

Physical examination will not be recorded in the CRF, any findings will appear in medical history or adverse events. The date of physical examination will be listed in a listing.

18.6. OTHER SAFETY ASSESSMENTS

18.6.1. IMMUNOGENICITY PROFILES ANALYSES

The following parameter will be summarized for immunogenicity:

1) Total Insulin Antibodies
    - Percent Binding (% B/T)
    - Positive/Negative
2) Cross Reactive Insulin Antibodies
    - Percent Binding (% B/T)
    - Positive/Negative
3) Insulin (Drug), Specific Antibodies
    - Percent Binding (% B/T)

Descriptive statistics will be tabulated by treatment and by timepoint for the continuous variables. Change from baseline to post-baseline timepoints will also be presented. The same MMRM model as the primary efficacy analysis (without imputing missing data and excluding the basal insulin dosing time)) will be used. Estimates of the means, LSMeans (SE and 2-sided 95% CIs) as well as treatment difference at each visit will be presented. Analyses will be done on the Safety Population.

The dichotomous outcomes will be summarized with frequency and percentage at scheduled visits. Treatment comparison will be performed using Fisher's exact test. P-value for the two-sided test will be presented.

Potential immunogenicity effect on local and systematic allergic reaction, hypersensitivity, and severe hypoglycaemia will be explored by summarizing those incidences between the treatment groups among subjects with post-baseline positive response of cross reactive antibodies. The local and system allergic reactions as well as the hypoglycaemia are found directly on the CRF, the hypersensitivity events will be found in the coded adverse events with the following specifications:

- System Organ Class (SOC): Immune system disorders
- High Level Group Term (HLGT): Allergic conditions
- High Level Term (HLT): Allergies to foods, food additives, drugs and other
- Preferred Term (PT): Drug hypersensitivity
- Lower level term (LLT): Drug hypersensitivity

The possible insulin neutralization effect will also be explored by presenting:

- The incidence of patients with increase over 10% in cross reacting antibody from baseline at any visit
- The incidence of patients with increases of HbA1c over 0.2% increase from baseline at any visit
- The incidence of patients with increase in total or basal insulin dose at any visit.

Treatment group comparisons will be performed by using a Chi-Square test, if 80% of the cells have an expected frequency >=5 otherwise Fisher's exact test will be used.

The immunogenicity and PK data will not be available at the time of database lock for the analysis. However the treatment will remain blinded during the laboratory assay. These data will be locked later and statistical analysis will be performed according to pre-specified method in this SAP.

18.6.2. 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, nocturnal hypoglycemia. Patients will be instructed to record all hypoglycemic events in the patient's 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.

The classification will be derived as follows:

- Severe: the patients entered in the eCRF: "severe (external assistance required to resolve event)"
- Documented Symptomatic Hypoglycemia: the patient entered in the eCRF: symptomatic and checked the "glucose value was less than or equal to 70 mg/dL".
- Asymptomatic Hypoglycemia: the patient entered in the eCRF: asymptomatic (symptoms of hypoglycemia not present) and checked the "glucose value was less than or equal to 70 mg/dL".
- Probable Symptomatic Hypoglycemia: the patient entered in the eCRF: symptomatic and checked the "glucose was not measured".
- Relative Hypoglycemia: the patient entered in the eCRF: asymptomatic or symptomatic and checked the "glucose value was over 70 mg/dL".
- Nocturnal Hypoglycemia: the patient has any of the 5 types above and also checked the "Nocturnal" time of the event.

Hypoglycemia event 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. The baseline hypoglycemia period is defined from the run-in period until randomization day. This rate will also be calculated per patient for nocturnal hypoglycemia episodes.

Hypoglycemia event rate per patient per 30 days will be analyzed using the same MMRM model as for the primary efficacy parameter (without imputing any missing data).

For change from baseline of hypoglycemia rate, a graphical display at scheduled visits, of LSMeans

and 2-sided 95% CI will be generated from the MMRM model. Additionally, mean (+/- SD) for actual measurements by visit will also be presented.

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.

19. STUDY DATA TECHNICAL CONFORMANCE

The data will be submitted using the Clinical Data Interchange Standards Consortium (CDISC). The Study Data Tabulation Model (SDTM) data will use version 1.4 (SDTMIG). The derived datasets will follow the Analysis Data Model (ADAM) and will use version 1.1 (ADAMIG).

20. DATA NOT SUMMARIZED OR PRESENTED

Not applicable.

21. REFERENCES

Yan, X., Lee, S., and Li, N. (2009), "Missing Data Handling Methods in Medical Device Clinical Trials," Journal of Biopharmaceutical Statistics, 19, 1085–1098. [392]

APPENDIX 1. REPORTING CONVENTIONS

Page Layout:

The Section 14 tables and Appendix 16 listings should be in landscape orientation by default.

The output in Section 14 and Appendix 16 will be in RTF file formal using Courier New font with 8 point size.

Statistical conventions:

The patient percentages (%) should be rounded to a whole number, with SAS rounding options used to obtain the values.

Percentages for values in the tables that are less than <1 should be presented as "<1".

If "%" is part of the column heading, do not repeat the "%" sign in the body of the table.

If a value is zero (0), then do not use 0% and leave the corresponding percentage blank.

The format for range should always be "Min, Max".

If there are missing data, then a missing row will be added to keep track of all patients. If there are no missing data, then delete the missing row. Percentages will not be presented on the missing category row.

Standard Deviation should be abbreviated as "SD", and Standard Error should be abbreviated as "SE"; it is presented within parenthesis next to the mean value, without any +/- sign. The Standard Deviation or Standard Error should have one additional decimal point beyond that of the mean (for example, if the mean has one decimal point, SD/SE should have two decimal points). Mean and median should have one additional decimal point beyond that of the data being summarized.

"N" will represent the entire treatment group, while "n" will represent a subset of the treatment group. For tables with population designated as a row heading, "N" should be used (i.e. tables where all the participant data is not available for every variable within a treatment group). As a guideline, if the number is used in denominator that it should be presented as "N". If the number is used in numerator it should be presented as "n".

P-values will be presented with 4 decimals.

APPENDIX 2. 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

START DATE	STOP DATE	ACTION
		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

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 3. SAS CODE EXAMPLE FOR MULTIPLE IMPUTATION

```
/* First, generate enough data to produce a monotone missing data pattern */
/* MCMC does not work with class statement. Pooled investigator sites and */
/* baseline insulin dose time have been converted to indicator variables  */
/* For pooled investigator sites (sitegr1n),                              */
/* let say that x is the total number of                                  */
/* pooled investigator sites.  Then, for pooled investigator sites #1,    */
/* inv01=1, inv02=0, …, inv0[x-1]=0                                       */
/* For pooled investigator sites #2, inv01=0, inv02=1, …, inv0[x-1]=0     */
/* For pooled investigator sites #[x-1], inv01=0, inv02=0, …, inv0[x-1]=1 */
/* For pooled investigator sites #x, inv01=0, inv02=0, …, inv0[x-1]=0     */
/* For baseline insulin dose (strata) time= morning, binstime=1           */
/* For baseline insulin dose time= evening, binstime=0                    */
/* No rounding or range is applied for any variable                       */
/* Non-informative prior is proc mi default MCMC prior information        */
/* 200 is proc mi default number of burn-in iterations                    */

proc mi data = <<insert input dataset name>> out = datamono
        seed =20171220
        NIMPUTE=100;
   by trtpn;
   var inv01 inv02 … inv0[x-1] binstime HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
   mcmc impute = monotone chain= multiple;
run;


/* Then, do full imputation based on sequential regression models         */
/* assuming monotone missing pattern.                                     */
proc mi data = datamono seed = 171016 out = datami NIMPUTE = 1;
   by _imputation_;
   class trtp strata sitegr1;
   var trtp strata sitegr1 HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
   monotone regression;
run;


/* Compute Changes from Baseline and create one categorical variables for */
/* the pooled investigational sites based on the [x-1] indicator pooled   */
/* investigational site variables                                         */
data datmichg;
   set datami (in=a drop = HbA1c_WK18 rename = (HbAc1_WK12 = result))
       datami (in=b drop = HbA1c_WK12 rename = (HbAc1_WK18 = result));

   * Visit;
   if a then visit = "Week 12";
      else if b then visit = "Week 18";
```

```
   * Change from baseline;
   change = result - HbA1c_BASE;

run;

/* MMRM Analysis by _imputation_ */

proc sort data=datmichg;
   by _imputation_;
run;

proc mixed data = datmichg method = REML order=internal;
   by _imputation_;
   class trtp(ref="Process V") strata sitegr1 avisit usubjid;
   model change = HbA1c_BASE trtp strata avisit sitegr1 trtp*avisit / DDFM =
   KR;
   repeated avisit / type = UN subject = usubjid;
   lsmeans trtp*avisit /diff cl;
   ods output diff = lsdiffs(where=(trt= 'Process IV' and _trt='Process V' and
   visit=_visit));
run;

/* Combine LSmean Differences for Visit 'Week 12' */
proc mianalyze parms(classvar = full) = lsdiffs (where = (visit = 'Week 12'));
   class trtp*avisit;
   modeleffects trtp*pvisit;
run;

/* Combine LSmean Differences for Visit 'Week 18' */
proc mianalyze parms(classvar = full) = lsdiffs (where = (visit = 'Week 18'));
   class trtp*avisit;
   modeleffects trtp*avisit;
run;
```

Note to programmers: In case of non-convergence or non-estimability issues for the generation of enough data to produce a monotone missing data pattern, replace the two proc mi by the following:

```
proc mi data = impute3 out = datamono seed =20171220 NIMPUTE=100
  round = 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
  min   = 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
  max   = 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1;
  var trtpn  binstime inv01 inv02 inv03 inv04 inv05 inv06 inv07 inv08 inv09
inv10 inv11 inv12 inv13 HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
  mcmc impute = monotone chain= multiple /*prior=ridge=p*/;
run;
```

```
proc mi data = datamono seed = 171016 out = datami NIMPUTE = 1;
  by _imputation_;
  class trtp strata sitegr1;
  var trtp strata sitegr1 HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
  monotone regression;
run;
```

APPENDIX 4. SAS CODE EXAMPLE FOR TIPPING POINT

```
/*An MNAR version of the MI procedure from Appendix 3 will be used.
  The SHIFT value will start at 0.01 and be incremented until the critical
value for non-inferiority of 0.4 is surpassed.  In particular, the upper limit
of the 95% confidence interval of the treatment difference will be calculated
for each iteration of the 0.01 increase to the MNAR adjustment and once it
surpasses 0.4, we take that MNAR adjustment value as k.    */


/* The first part gives a monotone patern to the data                    */
/* It imputes the holes in the data but leave empty the missings at the  */
/* end for discontinued patients                                         */

Proc mi data= <<insert input dataset name>> out=datamono
        seed=20171220
        NIMPUTE=100;
    by trtp;
    var inv01 inv02 … inv13 binstime HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
    mcmc impute = monotone chain= multiple;
run;

/* This part gives the imputation at the end of data                  */
/* Experimental treatment is trtpn=2, control treatment is trtpn=1    */
/* The shifts are done on AVAL not the CHG therefore we substract     */
/* a positive shift to the control making it harder to obtain         */
/* non-inferiority and at the same time add a positive shift to the   */
/* experimental treatment                                             */


proc sort data=datamono;
  by _imputation_;
run;
```

```
proc mi data = datamono out = datamono2
        seed =20171220
        NIMPUTE=1;
by _imputation_;
   class trtpn strata sitegr1;
   monotone reg;
    MNAR    Adjust (<HbA1c_WK18>/SHIFT= +Kprime ADJUSTOBS=(trtpn='2'))
            Adjust (<HbA1c_WK18>/SHIFT= -Kprime  ADJUSTOBS=(trtpn='1'));

   Var trtpn strata sitegr1 HbA1c_BASE HbA1c_WK12 HbA1c_WK18;
   ;
run;
```

Where Kprime is the shift value starting at 0.01 and ending at k.

```
proc mixed data= <<dataset>> method=REML order=internal;
   by shift_imputation_;
   class trtp(ref="Process V") strata sitegr1 avisit usubjid;
   model change= HbA1c_BASE trtp strata avisit sitegr1 trtp*avisit/DDFM=KR;
   repeated avisit/type=UN subject=usubjid;
   lsmeans trtp*avisit/diffcl;
run;
```