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16. Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol Version / Amendment	Date
Version 1.0	08 Sep 2017
Version 2.0	11 Jan 2018

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MYL-1501D-3004 CLINICAL STUDY PROTOCOL

Protocol Title	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
Product	MYL-1501D (Mylan's Insulin Glargine)
Protocol No.	MYL-1501D-3004
Study Type	Phase 3
Version	Final
Protocol Date	08 Sep 2017 **Revision Date** N/A
IND No.	IND 105279
Sponsor	Mylan GmbH Thurgauerstrasse, 40 CH 8050 Zürich, Switzerland

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SIGNATURE PAGE

Protocol Description	MYL-1501D-3004
Product Code	MYL-1501D
Protocol Version	Final
Protocol Version Date	18 SEP 2017

I have read this protocol and affirm that the information contained herein is complete and accurate.

Date: 18-SEP-2017

Global Lead, Safety Surveillance & Risk Management
Dr. Dhaval Panchal, MD

Date: 19-Sep-2017

Senior Director, Biometrics
Dr. Hans-Friedrich Koch, PhD

Date: 18-Sep-2017

Director, Global Clinical Operations
Keri Vaughan

Date: 18/09/2017

Global Clinical Director
Dr. Yaron Raiter, MD

Date: 18/09/2017

Head, Global Clinical Research and Development
Dr. Abhijit Barve, MD, PhD

PROTOCOL SYNOPSIS

Protocol Title	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
Background and Rationale	MYL-1501D is being developed as a follow-on biologic to the reference product Lantus® (insulin glargine). A phase 1 PK/PD study comparing MYL-1501D with Lantus® sourced from Europe and U.S. demonstrated PK and PD equivalence between the 3 products. PK/PD equivalence was also demonstrated with MYL-1501D product produced using two manufacturing processes (Process V and Process VI). The aim of this study is to demonstrate similar efficacy and safety between MYL-1501D products produced from two manufacturing processes (Process V and Process VI) in combination with insulin lispro in patients with type 1 diabetes mellitus (T1DM).
Primary Objectives	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 change in HbA1c from baseline to week 18 when administered in combination with mealtime insulin lispro.
Primary endpoints	The primary efficacy endpoint is change in HbA1c from baseline to week 18 for the ITT analysis set.
Methodology and treatments	This is a multicenter, double-blind, randomized, parallel-group phase 3 study in subjects with T1DM comparing the efficacy, immunogenicity and safety of MYL-1501D products from two manufacturing processes (Process V and Process VI). After up to 2-week screening period, all subjects will be titrated on Lantus® during a 4-week run-in period, and will be shifted from their current mealtime insulin to Humalog®. The subjects will be randomized (stratified by 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 study will be conducted in the US. Approximately 110 sites will be included in the study.
Inclusion/ exclusion criteria	**Inclusion criteria** 1. Written and signed informed consent needs to be provided by subjects or their legal representatives before starting any protocol-specific procedures. 2. Male and female subjects between the ages of 18 to 65 years, both ages inclusive. 3. Subjects with an established diagnosis of T1DM per ADA 2017 criteria who also fulfil the following criteria: a. Initiation of insulin treatment within 6 months of T1DM

diagnosis

b. Treatment with basal-bolus insulin therapy for at least 1 year before screening
c. Fasting plasma C-peptide <0.3 nmol/L at screening
d. Subject has been on once daily Lantus® at stable dose (±15% variation in dose) for at least 3 months at screening

4. Body mass index (BMI) of 18.5 to 35 kg/m^2 at screening (both values inclusive).
5. Stable weight, with no more than 5 kg gain or loss in the 3 months prior to screening, this information will be collected by subject interview during medical history.
6. Glycosylated hemoglobin (HbA1c) ≤ 9.5% at screening.
7. Hemoglobin ≥9.0 g/dL at screening.
8. Subject has the capability of communicating appropriately with the investigator.
9. Subject is able and willing to comply with the requirements of the study protocol including the 8-point self-monitored blood glucose (SMBG), completion of subject diary records and following a recommended diet and exercise plan for the entire duration of the study.
10. Female subjects of childbearing potential who are willing to use oral contraception or two acceptable methods of contraception, (e.g., intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.), from the time of screening and for the duration of the study, through study completion.
    a. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    b. Postmenopausal females must have had no regular menstrual bleeding for at least 1 year prior to screening.
    c. Female subjects who report surgical sterilization must have had the procedure at least 6 months prior to screening.
    d. All female subjects of childbearing potential must have negative pregnancy test results at screening and at clinic visits, as per the SCHEDULE OF ACTIVITIES (SOA).
    e. If female subjects have male partners who have undergone vasectomy, the vasectomy must have occurred more than 6 months prior to screening

Exclusion Criteria

1. History or presence of a medical condition or disease that in the investigator's opinion would place the subject at an unacceptable risk from study participation.
2. History of hypersensitivity to any of the active or inactive ingredients of the insulin/insulin analogue preparations used in the study, OR history of significant allergic drug reactions.
3. History of use of animal insulin within the last 3 years or use of approved biosimilar insulin glargine at any time prior to study entry, except for subject who previously participated in MYL-1501D studies and were compliant with the study protocols.
4. History of use of a regular immunomodulator therapy in the 1 year prior to screening.

	5. History of autoimmune disorders other than T1DM or insufficiently treated autoimmune thyroid disorders judged clinically relevant by the investigator (recorded while collecting subject history). 6. History of ≥1 episodes of diabetic ketoacidosis or emergency room visits for uncontrolled diabetes leading to hospitalization within the 6 months prior to screening. 7. History of clinically significant acute bacterial, viral or fungal systemic infections in the last 4 weeks prior to screening (recorded while collecting subject history). 8. Any clinically significant abnormality in electrocardiogram (ECG) or safety laboratory tests (LFT, RFT, hematology or any other laboratory deemed clinically relevant by the investigator) conducted at screening and considered by the investigator to make the subject ineligible for the study. 9. Serological evidence of human immunodeficiency virus (HIV), hepatitis B surface antigen (HbSAg) or hepatitis C antibodies (HCVAb) at screening. 10. History of drug or alcohol dependence or abuse during the 1 year prior to screening. 11. Receipt of another investigational drug in the 3 months prior to screening (or as per local regulations), or if the screening visit is within 5 half-lives of another investigational drug received (whichever is longer), or scheduled to receive another investigational drug during the current study period. 12. Subjects with the following secondary complications of diabetes: a. Active proliferative retinopathy as confirmed by a dilated ophthalmoscopy examination / retinal photography (performed by a person legally authorized to do so) within the 6 months prior to screening. b. Clinical nephrotic syndrome or diabetic nephropathy with a serum creatinine level >1.5 times of upper limit of reference range at screening c. History of severe form of neuropathy or cardiac autonomic neuropathy, recorded while collecting subject history. Subject's with mild or moderate forms of neuropathy will be allowed. d. Subjects with a history of limb amputation as a complication of diabetes (at any time), or any vascular procedure during the 1 year prior to screening. e. History of diabetic foot or diabetic ulcers in the 1 year prior to screening. 13. Any elective surgery requiring hospitalization planned during the study period. 14. Clinically significant major organ disorder at the time of screening including:

	a. Uncontrolled hypertension, defined as stage 2 hypertension by Joint National Committee VII (even if therapy is ongoing, blood pressure ≥160 mm Hg systolic or ≥100 mm Hg diastolic). b. Uncontrolled hyperlipidemia (even if therapy is ongoing, LDL >160 mg/dL or triglycerides >500 mg/dL). c. Uncontrolled hyperthyroidism or hypothyroidism (subjects can be included if these conditions are controlled with thyroid hormones or anti-thyroid drugs). d. Impaired hepatic function (alanine transaminase [ALT] or aspartate transaminase [AST] value >2 times the upper limit of the reference range and/or serum bilirubin 1.5 times the upper limit of the reference range at the screening visit). Subjects with evidence of Gilberts disease may be included in the study if they have total bilirubin of <3 mg/dL with indirect bilirubin contributing to >80% of the total bilirubin. 15. History of a significant medical condition, such as: a. Clinically significant cardiac disease like unstable angina, myocardial infarction, grade 3 or 4 congestive heart failure (CHF) according to New York Heart Association criteria, valvular heart disease, cardiac arrhythmia requiring treatment, and pulmonary hypertension; during the year prior to screening. b. Stroke or transient ischemic attack (TIA) in the 6 months before screening. 16. Subjects with major depressive illness in the last 3 years (those who have well-controlled depression for 3 months on a stable dose of antidepressants, with no major depressive episodes in the last 3 years, can be included, even if they are on medication), subjects with history of other severe psychiatric diseases (manic depressive psychosis [MDP], schizophrenia), which in the opinion of the investigator precludes the subject from participating in the study (recorded while collecting subject history). 17. History of hematological disorders that can affect the reliability of HbA1c estimation (hemoglobinopathies, hemolytic anemia, sickle cell anemia, etc.). 18. Subjects using the following in the 3 months prior to screening: a. Insulin pump therapy b. Any anti-diabetic drugs other than the study insulins allowed by the protocol. 19. Moderate insulin resistance, defined as requiring insulin of ≥1.5 U/IU/kg/day. 20. Subjects who have received ≥14 consecutive days of glucocorticoid therapy by oral, intravenous, inhaled or other routes that produce systemic effects within the past 1 year, or who have received steroids by any route (except intra-nasal, intra-ocular, and topical) within the 4 weeks immediately preceding screening.

	21. Subjects diagnosed as having cancer (subjects with history of basal cell carcinoma, carcinoma in situ or squamous cell cancer of skin, or in remission >5 years, will be allowed). 22. Subjects who have donated blood or plasma in the 1 month prior to screening
Sample size	A total of 202 subjects with T1DM are planned to be randomized for this study and will receive either MYL-1501D Process V product or MYL-1501D Process VI product, in a 1:1 ratio. The sample size estimation is based on assumptions for the change from baseline up to week 18 in HbA1C with either MYL-1501D product from Process V or Process VI. It is assumed, that true mean groups mean difference is 0.03 and standard deviation is equal to 0.74. To demonstrate non-inferiority margin of 0.4% using a 2-sided 95% confidence interval and a 90% power, a total of 172 subjects (86 subjects per treatment group) are required. To account for a maximum of 15% of subjects being not eligible for the per protocol analysis, a total sample size of 202 is planned to be randomized for this study. The true treatment difference and standard deviation is based on previous study MYL-GAIA-3001.
Statistical Methods	A repeated measures analysis employing a restricted maximum likelihood (REML)-based, mixed model repeated measures (MMRM)-effects model approach will be used to estimate a 95% confidence interval for the absolute difference between MYL-1501D Process V product and MYL-1501D Process VI product for mean change in HbA1c at Week 18. Non-inferiority for primary objective will be established if the upper limit of a two sided 95% confidence interval for the absolute difference (MYL-1501D Process VI minus MYL-1501D Process V) of mean change from baseline for HbA1c is no greater than 0.4% at 18 weeks of treatment.

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LIST OF COMMONLY USED ABBREVIATIONS

ADA	American Diabetes Association
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
bpm	beats per minute
cm	centimeter
CI	Confidence interval
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of Variation
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HbSAg	Hepatitis B Surface Antigen
HCVAb	Hepatitis C antibodies
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IRB	Institutional Review Board
IVRS/IWRS	Interactive Voice Response System/ Interactive Web Response System
ITT	Intent to treat
kg	kilogram
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Milliliter
MMRM	Mixed Model Repeated Measures
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PSRM	Product Safety and Risk Management
SMBG	Self-monitored blood glucose
REML	Restricted maximum likelihood
RIPA	Radioimmunoprecipitation assay
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SID	Subject Identification
SMBG	Self-monitored blood glucose
SOA	Schedule of Activities
SOP	Standard Operating Procedure
T1DM	Type 1 diabetes mellitus
TEAE	Treatment emergent adverse event
US	United States
WoCBP	Women of Child-Bearing Potential

1 STUDY DIAGRAM AND STUDY SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Conduct Section (Section 6) for detailed information on each procedure and assessment required for compliance with the protocol.

Figure 1: Study Diagram

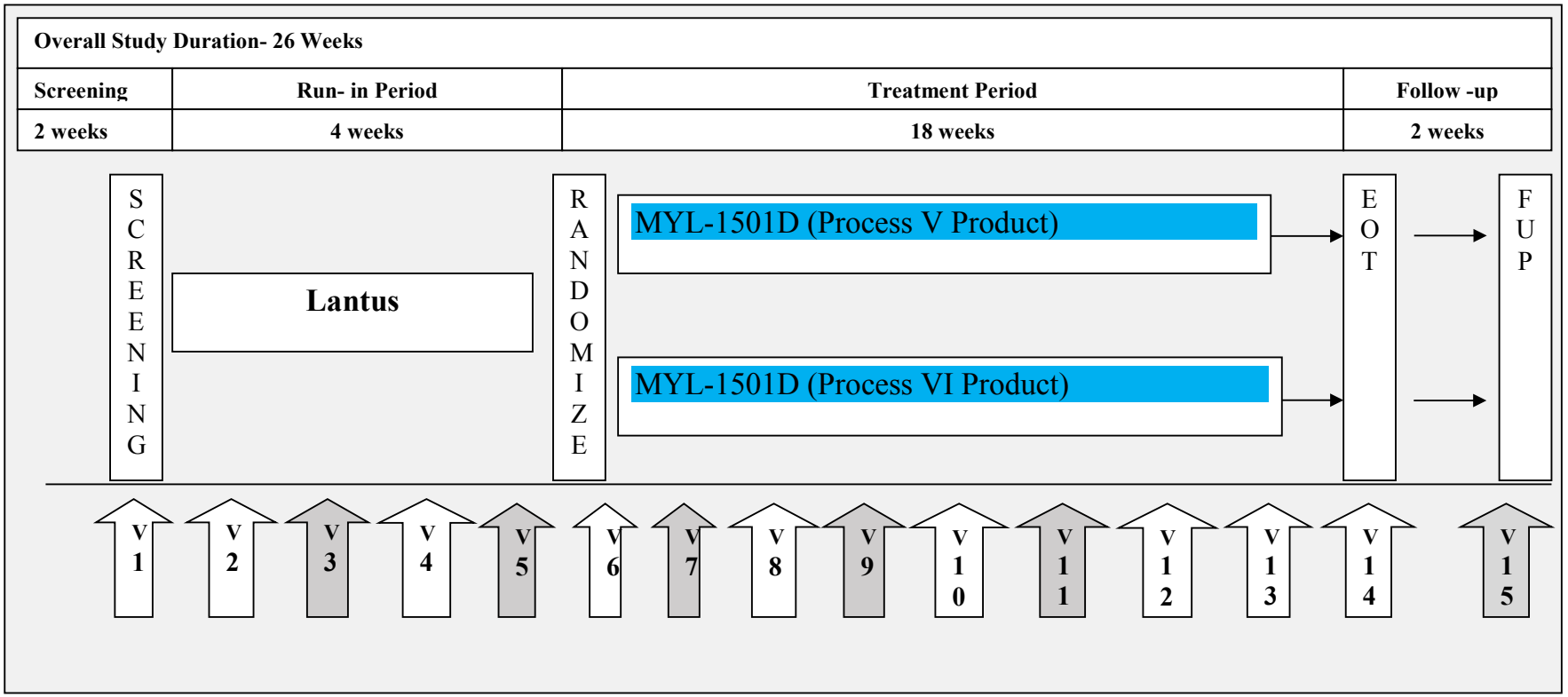

Table 1: Study Schedule of Activities

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									Follow-up
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	

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									Follow-up
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
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	
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	

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									Follow-up
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
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.

2 INTRODUCTION

2.1 Indication

MYL-1501D is being developed as a follow-on biologic (US terminology) or biosimilar (EU terminology) to Lantus®.

2.2 Background and Rationale

Insulin secretion in healthy subjects is characterized by relatively constant basal insulin secretion with a post-prandial surge. Type 1 diabetes mellitus (T1DM) is characterized by loss of the insulin-producing beta-cells of the islets of Langerhans in the pancreas, leading to a deficiency of insulin. The main cause of beta-cell loss is a T-cell mediated autoimmune attack [1]. The principal treatment of patients with T1DM is initiation of insulin and diet control and careful monitoring of blood glucose levels.

The Diabetes Control and Complications Trial [2] and other trials [3] provide conclusive evidence that maintaining tight glycemic control can prevent or delay microvascular and macrovascular complications in patients with T1DM. A number of different insulin regimens have been proposed for treatment of patients with T1DM. It is generally accepted that the so-called basal-bolus insulin regimen (1 or 2 daily injections of long/intermediate-acting insulin covering basal insulin requirements in combination with 3 daily injections of short-/rapid acting insulin to cover meal-related insulin requirements) generally yields the best glycemic control in diabetes. Clear targets for plasma glucose levels have been recommended for basal-bolus insulin regimens [4].

Different insulin preparations are available for management of basal insulin requirements, including intermediate-acting insulins (neutral protamine Hagedorn insulin) and long-acting insulin analogs such as insulin glargine and insulin detemir. Long-acting insulin analogs have proven efficacy and offer good glucose control over 24 hours for a single dose. Insulin glargine is a long-acting insulin analogue allowing once-daily administration to cover basal insulin requirements for over 24 hours. After injection of Insulin glargine into the subcutaneous tissue, the acidic solution is neutralized; leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration versus time profile with a prolonged duration of action.

MYL-1501D is a human insulin analogue of r-DNA origin produced in the host organism *Pichia pastoris*. *P pastoris* is a methylotropic yeast that has been successfully used in the production of proteins.

The aim of this study is to demonstrate similar efficacy and safety between MYL-1501D product produced from two manufacturing processes in combination with insulin lispro in patients with T1DM.

Since the two investigational products have an identical presentation of prefilled pen to be used by the subjects during the treatment period, the subject and the treating physician will remain blinded to treatment assignment. Furthermore, the evaluation of the study endpoints, such as analysis of immunogenicity and glycosylated hemoglobin (HbA1c), will be performed in a blinded manner by blinded personnel. The sponsor team as well as the CRO team will also be blinded to the subject assigned treatment.

To ensure that both treatment arms are comparable at baseline with respect to drug-induced immune responses and other parameters, only subjects who have been on a stable dose of Lantus® for at least 3 months prior to screening will be included.

During the 4-week run-in period with Lantus® and Humalog®, the dose of insulin will be titrated (if required) to ensure diabetes control. The run-in period ensures comparable drug exposure for all subjects, and increases the likelihood of comparable immune responses at the start of the treatment period. An 18-week treatment period is an adequate period to detect differences in HbA1c of the treatment arms [5].

Dosing with MYL-1501D during treatment period and Lantus® during run-in period will be guided by self-monitored blood glucose (SMBG)-based glucose level assessments, as suggested in the dosing algorithm.

Rescue criteria based on HbA1c are defined based on week 12 HbA1c measurement, so that a potential worsening of metabolic control in subjects during the study can be identified and therapy modified at the discretion of the investigator.

A follow-up visit, 2 weeks after the end of treatment, will ensure the safety of all subjects after they stop the study medication and return to receiving approved medications.

Complete information for the study medication can be found in MYL-1501D Investigator's Brochure (IB). [6]

2.2.1 Rationale for Dose Selection

Only subjects who have been on a stable dose of Lantus® for at least 3 months prior to screening will be included in the study, thus subjects would be on a stable dose at study entry. If required, subject dose should be adjusted during the 4-week run-in period to stabilize the subjects. During the treatment period, dose adjustment should be avoided but it is permitted to ensure subject's stable state and safety.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objectives

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 change in HbA1c from baseline to week 18 when administered in combination with mealtime insulin lispro.

3.1.2 Other objectives

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 SMBG profile from baseline

3.2 Endpoints

3.2.1 Primary Endpoints

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

3.2.2 Secondary Endpoints

3.2.2.1 Efficacy

- Change in fasting plasma glucose from baseline
- Change in basal insulin, meal-time, and total insulin dose per unit body weight (U/kg) from baseline
- Change in 8-point SMBG profile from baseline

3.2.2.1 Safety

- Incidence of positive antibody response and change in antibody percentage binding from baseline.
- Change in hypoglycemia rate (30 day adjusted) from baseline and incidence of hypoglycemic events
- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Incidence of local reactions, systemic reactions and other adverse events
- Incidence of device-related safety assessment

4 STUDY POPULATION

4.1 Study Population

A total of 202 subjects with T1DM are planned to be randomized in this study, to receive MYL-1501D from either Process VI or Process V with a randomization ratio of 1:1.

A detailed description related to sample size determination is provided in Section 7.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Written and signed informed consent needs to be provided by subjects or their legal representatives before starting any protocol-specific procedures.
2. Male and female subjects between the ages of 18 to 65 years, both ages inclusive.
3. Subjects with an established diagnosis of T1DM per American Diabetes Association (ADA) 2017 criteria who also fulfil the following criteria:
    a. Initiation of insulin treatment within 6 months of T1DM diagnosis
    b. Treatment with basal-bolus insulin therapy for at least 1 year before screening
    c. Fasting plasma C-peptide <0.3 nmol/L at screening
    d. Subject has been on once daily Lantus® at stable dose (±15% variation in dose) for at least 3 months at screening
4. Body mass index (BMI) of 18.5 to 35 kg/m2 at screening (both values inclusive).
5. Stable weight, with no more than 5 kg gain or loss in the 3 months prior to screening, this information will be collected by subject interview during medical history.
6. HbA1c ≤9.5% at screening.
7. Hemoglobin ≥9.0 g/dL at screening.
8. Subject has the capability of communicating appropriately with the investigator.
9. Subject is able and willing to comply with the requirements of the study protocol including the 8-point SMBG, completion of subject diary records and following a recommended diet and exercise plan for the entire duration of the study.
10. Female subjects of childbearing potential who are willing to use oral contraception or two acceptable methods of contraception, (e.g., intra-uterine device plus condom, spermicidal

gel plus condom, diaphragm plus condom, etc.), from the time of screening and for the duration of the study, through study completion.

a. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

b. Postmenopausal females must have had no regular menstrual bleeding for at least 1 year prior to screening.

c. Female subjects who report surgical sterilization must have had the procedure at least 6 months prior to screening.

d. All female subjects of childbearing potential must have negative pregnancy test results at screening and at clinic visits, as per the SCHEDULE OF ACTIVITIES (SOA).

e. If female subjects have male partners who have undergone vasectomy, the vasectomy must have occurred more than 6 months prior to screening

4.2.2 Exclusion Criteria

Subject candidates must not be enrolled in the study if they meet any of the following criteria:

1. History or presence of a medical condition or disease that in the investigator's opinion would place the subject at an unacceptable risk from study participation.

2. History of hypersensitivity to any of the active or inactive ingredients of the insulin/insulin analogue preparations used in the study, OR history of significant allergic drug reactions.

3. History of use of animal insulin within the last 3 years or use of approved biosimilar insulin glargine at any time prior to study entry, except for subject who previously participated in MYL-1501D studies and were compliant with the study protocols.

4. History of use of a regular immunomodulator therapy in the 1 year prior to screening.

5. History of autoimmune disorders other than T1DM or insufficiently treated autoimmune thyroid disorders, judged clinically relevant by the investigator (recorded while collecting subject history).

6. History of ≥1 episodes of diabetic ketoacidosis or emergency room visits for uncontrolled diabetes leading to hospitalization within the 6 months prior to screening.

7. History of clinically significant acute bacterial, viral or fungal systemic infections in the last 4 weeks prior to screening (recorded while collecting subject history).

8. Any clinically significant abnormality in electrocardiogram (ECG) or safety laboratory tests (LFT, RFT, hematology or any other laboratory deemed clinically relevant by the investigator) conducted at screening and considered by the investigator to make the subject ineligible for the study.

9. Serological evidence of human immunodeficiency virus (HIV), hepatitis B surface antigen (HbSAg) or hepatitis C antibodies (HCVAb) at screening.

10. History of drug or alcohol dependence or abuse during the 1 year prior to screening.

11. Receipt of another investigational drug in the 3 months prior to screening (or as per local regulations), or if the screening visit is within 5 half-lives of another investigational drug received (whichever is longer), or scheduled to receive another investigational drug during the current study period.

12. Subjects with the following secondary complications of diabetes:

    a. Active proliferative retinopathy as confirmed by a dilated ophthalmoscopy examination / retinal photography (performed by a person legally authorized to do so) within the 6 months prior to screening.

    b. Clinical nephrotic syndrome or diabetic nephropathy with a serum creatinine level >1.5 times of upper limit of reference range at screening

    c. History of severe form of neuropathy or cardiac autonomic neuropathy, recorded while collecting subject history. Subjects with mild or moderate forms of neuropathy will be allowed.

    d. Subjects with a history of limb amputation as a complication of diabetes (at any time), or any vascular procedure during the 1 year prior to screening.

    e. History of diabetic foot or diabetic ulcers in the 1 year prior to screening.

13. Any elective surgery requiring hospitalization planned during the study period.

14. Clinically significant major organ disorder at the time of screening including:

    a. Uncontrolled hypertension, defined as stage 2 hypertension by Joint National Committee VII (even if therapy is ongoing, blood pressure ≥160 mm Hg systolic or ≥100 mm Hg diastolic).

    b. Uncontrolled hyperlipidemia (even if therapy is ongoing, LDL >160 mg/dL or triglycerides >500 mg/dL).

    c. Uncontrolled hyperthyroidism or hypothyroidism (subjects can be included if these conditions are controlled with thyroid hormones or anti-thyroid drugs).

    d. Impaired hepatic function (alanine transaminase [ALT] or aspartate transaminase [AST] value >2 times the upper limit of the reference range and/or serum bilirubin 1.5 times the upper limit of the reference range at the screening visit). Subjects with evidence of Gilberts disease may be included in the study if they have total bilirubin of <3 mg/dL with indirect bilirubin contributing to >80% of the total bilirubin.

15. History of a significant medical condition, such as:

a. Clinically significant cardiac disease like unstable angina, myocardial infarction, grade 3 or 4 congestive heart failure (CHF) according to New York Heart Association criteria, valvular heart disease, cardiac arrhythmia requiring treatment, and pulmonary hypertension; during the year prior to screening.

b. Stroke or transient ischemic attack (TIA) in the 6 months before screening.

16. Subjects with major depressive illness in the last 3 years (those who have well controlled depression for 3 months on a stable dose of antidepressants, with no major depressive episodes in the last 3 years, can be included, even if they are on medication), subjects with history of other severe psychiatric diseases (manic depressive psychosis [MDP], schizophrenia), which in the opinion of the investigator precludes the subject from participating in the study (recorded while collecting subject history).

17. History of hematological disorders that can affect the reliability of HbA1c estimation (hemoglobinopathies, hemolytic anemia, sickle cell anemia, etc.).

18. Subjects using the following in the 3 months prior to screening:

    a. Insulin pump therapy

    b. Any anti-diabetic drugs other than the study insulins allowed by the protocol.

19. Moderate insulin resistance, defined as requiring insulin of ≥1.5 U/IU/kg/day.

20. Subjects who have received ≥14 consecutive days of glucocorticoid therapy by oral, intravenous, inhaled or other routes that produce systemic effects within the past 1 year, or who have received steroids by any route (except intra-nasal, intra-ocular, and topical) within the 4 weeks immediately preceding screening.

21. Subjects diagnosed as having cancer (subjects with history of basal cell carcinoma, carcinoma in situ or squamous cell cancer of skin, or in remission >5 years, will be allowed).

22. Subjects who have donated blood or plasma in the 1 month prior to screening

4.2.3 Criteria for study drug termination, withdrawal from the study and study termination

Subjects will be free to request termination of study drug or withdrawal from the study at any time for any reason.

If, for any reason, a subject discontinues the study prematurely, the subject may be followed up upon consent and as detailed in the following withdrawal criteria.

Following are the withdrawal criteria:

1. Withdrawal of consent.

2. For female subjects, diagnosis of pregnancy or stated intention to become pregnant. Effort should be made by the site to obtain consent from the pregnant women, so that they are followed until delivery or termination.

3. At the investigator's discretion (following discussion with the sponsor medical monitor), for safety issues such as severe hypoglycemia or hypoglycemic unawareness. The site should request the subject consent to follow-up as per the SCHEDULE OF ACTIVITIES until the Week 20 (Follow-up visit).

4. At the investigator's discretion (following discussion with the sponsor medical monitor), in certain situations such as significant illness, hospitalization for surgery, or an SAE which in the opinion of the investigator warrants treatment withdrawal. The site should request the subject consent to follow-up as per the SCHEDULE OF ACTIVITIES until the Week 20 (Follow-up visit).

4.3 Contraception

4.3.1 Females - Non-childbearing Potential

Female subjects of non-childbearing potential must meet at least one of the following criteria:

1. Postmenopausal females, defined as:

   - Females who are 45-65 years of age who have been amenorrheic for at least 1 year **and** who are known to have a serum FSH level >30 IU/L in the absence of hormone replacement therapy.

2. Females who have a documented hysterectomy and/or bilateral oophorectomy.

All other females will be considered to be of childbearing potential.

4.3.2 Females - Childbearing Potential

Female subjects of child-bearing potential must use an acceptable, highly effective method of contraception (i.e. a method with a failure rate <1% when used consistently and correctly) starting from screening through to at least 7 days after the final dose of study drug. For this study, such methods include at least one of the following:

- Abstinence (periodic abstinence is not acceptable).
- Tubal ligation.
- Intrauterine device (IUD) of intrauterine system (IUS).
- Condom.
    - Depending on the region of study this may be with or without spermicidal foam/gel/film/cream/suppository.
- Male partner who has had a vasectomy for at least 6 months. Male partners with vasectomies of <6 months are NOT considered protected.
- Hormonal contraceptives (oral, injected, transdermal or implanted) with the exception of low dose gestagens, i.e. only containing lynestrenol or norethisterone, since they do not inhibit ovulation and are therefore not considered as highly-effective. The subject must remain on the hormonal contraceptive throughout the study and must have been

using hormonal contraceptives for an adequate period prior to the study to ensure effectiveness (e.g., 3 months).

4.4 Pregnancy Testing

Serum or urinary pregnancy testing will be performed on all females of childbearing potential as described in the schedule of activities (results will be reviewed and must be negative prior to dosing). In the event of a positive test, the subject will be withdrawn from the study (or will not enter the study if during screening).

Any pregnancy occurring after randomization to study drug will be followed up and reported to the sponsor as per Section 9.4.1.

5 STUDY DRUG

5.1 Investigational Drug

During Treatment period, subjects will be randomized to receive one of the following;

MYL-1501D Product from Process V (100 U/mL)

or

MYL-1501D Product from Process VI (100 U/mL)

Additional treatment drugs provided during the study which are not investigational study drugs are detailed below:

During the run-in period, subject will receive Lantus® from Sanofi-Aventis sourced from the US (US listed drug) 100 U/mL

All subjects will receive Humalog® (insulin lispro injection, 100 U/mL), manufactured by Eli Lilly throughout the study.

MYL-1501D will be packaged and labelled according to all local legal requirements.

Clinical Supplies will provide prepackaged supplies for each subject. A kit will be assigned at randomization using the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS).

A label will be attached to the outside of each kit. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Subject number/study center number
- Contents and quantity
- Lot number
- Randomization code/kit number
- Investigator name
- Storage instructions
- Caution statement (for clinical study use only)
- Expiry date
- Mylan's name and address

5.1.1 Administration of Study Drugs

During the **Run-in period,** all subjects will receive Lantus® from Sanofi-Aventis sourced from the US (US listed drug) 100 U/mL until randomization. In addition, all subjects will be shifted from their current mealtime insulin to Humalog® at the start of the run-in period, and will continue on this for the complete study. The doses of Lantus® and Humalog® will be titrated (if required) during the run-in period to ensure diabetes control.

During **Treatment period,** all subjects will receive one of the following treatments;

MYL-1501D product from Process VI or Process V. Both investigational products will be provided in a pre-filled disposable pen with a 3-mL cartridge. During the treatment period, dose titration will be kept to a minimum.

In addition, all subjects will receive Humalog® (insulin lispro injection, 100 U/mL), manufactured by Eli Lilly.

In the event of any significant dosing errors, the CRO contact person and/or CRO medical monitor, or Mylan study contact should be informed immediately.

5.2 Study Medication Complaints

In the event the subject has a complaint/concern during study participation regarding the medication supplied, they should contact the site.

In the event of a complaint/concern regarding any medication provided by Mylan for this study, at a minimum the following information should be sent by the site via e-mail to MGRG.study.medication.complaints@mylan.co.uk.

- Study number.
- Principal Investigator name.
- Subject ID.
- Date of occurrence of incident/complaint.
- Description of incident/complaint (facts).
- Confirmation if the complaint caused or resulted in a SAE? If "Yes", confirmation that the SAE has been reported.

Additional information and potentially the return of study medication may be requested by Mylan such that the complaint can be investigated.

5.3 Storage, Disposition of Unused Study Drug and Drug Accountability

The Investigator, or an approved representative, e.g. pharmacist, will ensure that all investigational products are stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements while at the investigator site.

Study drug should be stored in accordance with the drug label. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.

Temperature of storage facilities should be monitored and recorded on a daily basis using validated devices that record maximum and minimum temperatures. Should the storage facility experience any excursion of temperature outside of the labelled storage condition this must be reported immediately to Mylan or designee. At sites where daily monitoring and recording is not possible on weekends, the temperature record (e.g. max/min thermometers) should be checked immediately for any temperature excursions on the next working day after the weekend. Devices used for temperature monitoring should be regularly calibrated. Affected material must be placed into quarantine until the impact of the excursion has been assessed and confirmed by Mylan.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the study drug. Drug accountability forms must be used. Alternatively, Mylan

may approve use of standard institution forms. In either case, the forms must identify the study drug, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Mylan or designee.

At the end of the study, Mylan will provide instructions with regards to disposition of any unused investigational product. If Mylan authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Mylan. Destruction must be adequately documented.

5.4 Randomization

Assignment of Subject Identification number (SID), randomization number and study medication, as well as site drug inventory control will be managed by an automated IVRS/IWRS. A manual containing complete instructions for Web or telephone access and use will be provided to each site prior to study start. The IVRS/IWRS will assign a SID for each subject's first clinic visit. Each SID will be unique and serve as the primary subject identifier throughout all phases of the study. The SID must appear on all case report form (CRF) pages, source documents, laboratory data, ECG and diary data. Subjects qualifying to enter the study drug treatment phase, will be assigned an additional "randomization number" by the IVRS/IWRS at randomization. Dynamic allocation with minimization algorithm will be used for treatment randomization. Randomization will be stratified by investigator and basal insulin (Glargine) dose time (morning or evening).

5.5 Breaking the Blind

Regardless of the assigned treatment arm, all subjects in the study are provided with active anti-diabetic treatment, Insulin glargine.

The blinded treatment code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Qualified Investigator to complete a serious adverse event report or the clinical report. In such situations, the randomization information will be held by designated individual(s), and the date and reason for breaking the blind must be recorded. If possible, the CRO project manager should be contacted by telephone prior to unblinding but no later than 24 hours after unblinding. The investigator should follow the study's randomization procedures and should ensure that the code is broken only in accordance with the protocol. As the study is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s). Unblinding of treatment code for final data analysis will be done after database lock. Unblinding process will be performed in accordance to both sponsor's and CRO's unblinding SOPs, as detailed in the statistical analysis plan.

5.6 Concomitant Medications

All concomitant medications taken during the study (from signing informed consent to post-study follow-up) must be recorded with indication, daily dose, and start and stop dates of administration in the CRF. All subjects will be questioned about concomitant medication at each clinic visit and at follow up.

Medications taken within 28 days prior to screening and prior to dosing with study medication will be documented as a prior medication. Medications taken after dosing with study medication will be documented as concomitant medications.

Other than study drugs, insulin, insulin analogs and other anti-diabetes medications as well as glucocorticoid therapy (oral, intravenous, inhaled or other routes that produce systemic effects) are prohibited during the study (including the run-in period and the treatment period), except in case of rescue medication treatment.

A list of medications that may interfere with the effect of insulin is provided in Table 2. No drugs listed in this table should be started during the run-in period or treatment period.

Table 2: List of Prohibited Medication

Drug classes that are known to **augment** the blood glucose lowering effect of insulin such as:	Drugs and drug classes that are known to **decrease** the blood glucose lowering effect of insulin such as:
1. salicylates at doses more than >2 g/day 2. sulfa antibiotics 3. angiotensin converting enzyme inhibitors 4. disopyramide 5. fibrates 6. fluoxetine 7. monoamine oxidase inhibitors 8. propoxyphene 9. pentoxifylline 10. somatostatin analogs 11. bromergocryptine (bromocryptine) 12. anabolic steroids.	1. danazol 2. niacin 3. diuretics 4. sympathomimetic agents 5. glucagon 6. isoniazid 7. somatropin 8. thyroid hormones 9. oral contraceptives 10. estrogens 11. progestogens 12. protease inhibitors 13. phenothiazine derivatives 14. atypical antipsychotic medications (e.g. olanzapine and clozapine).

Subjects will abstain from all prohibited medications as described in the exclusion criteria section of this protocol (Section 4.3.2). Use of prohibited medication during the study will be deemed a protocol deviation and such subjects will be assessed by Mylan or designee regarding the potential need to early terminate study drug (e.g. for safety reasons: see Section 4.3.4).

5.7 Recommended Procedure for Subject Experiencing Adverse Effects Secondary to Excessive Pharmacological Effects of Study Drug

The following rescue criterion will be implemented to protect the safety of subjects during the study:

“Worsening of HbA1c by >1.0% compared to baseline at 12 weeks post randomization”.

If the subject meets the criterion the investigator can switch the subject to Lantus® provided as part of the study at week 15 (Visit 13) or earlier, and continue with the study activities and procedures until the end of the study.

6 STUDY CONDUCT

Subjects eligible for study recruitment will have the nature, purpose, and risks of the study explained to them by the investigator. They will be provided with a written copy of the informed consent form (ICF) for the study and given sufficient time to consider the study's implications before deciding to participate. Subjects agreeing to participate in the study will sign the ICF and be given a duplicate copy before undergoing any screening or pre-screening (if required) procedures. A unique SID will be issued at the time of consent by IVRS/IWRS system.

Once a subject enrolls in this study, the site will make every effort to retain the subject for the planned duration of the study. Clinical study site staff are responsible for developing and implementing support and retention plans. Elements of this plan may include the following.

- Thorough explanation of the complete clinical study visit schedule and procedural requirements during the informed consent process and re-emphasis at each clinic visit.
- A simple explanation of the key data and key time points that are critical for the study's successful analysis, and the importance of all the treatment groups to the overall success of the study.
- Discussion at screening, and subsequent regular review of possible barriers to clinic visit attendance and full study participation and compliance.
- Collection of contact information at screening (address, phone numbers, email), which is regularly reviewed at subsequent clinic visits.
- Use of appropriate and timely study visit reminders.
- Immediate and multifaceted follow-up on missed clinic visits, including the possible use of trained staff to complete in-person contact with subjects at their homes.

In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study. All contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the CRF. Regardless of site plans to support and retain subjects within the study, subjects may voluntarily withdraw from the study for any reason and at any time.

For a subject that completes the study and all procedures it is anticipated that the duration of study would be up to 26 weeks.

For details and timings of assessments, refer to Section 6.5.

6.1 Screening Procedures

Each prospective subject must agree to participate in screening procedures by signing the most recent ICF before any screening procedure is initiated. The Principal Investigator or

Medical Sub-Investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to enrolment.

6.1.1 Screening (Visit 1 [Week -6 to Week -4])

Subjects will commence screening procedures within 6 weeks prior to randomization, to confirm that they meet the selection criteria for the study. If the time between screening procedures and potential randomization exceeds 6 weeks as a result of unexpected delays, then the subject will need to be discussed with Mylan or designee to consider potential for re-screening (if re screening is agreed, the subject will need to be re consented and assigned a new SID via IVRS/IWRS). Re-screening for other reasons may be possible following discussion with the Mylan or designee. If re screening occurs this will be clearly documented within the site file.

The following will be completed in during the visit:

- Obtain written informed consent before any study-related procedure is initiated, including the cessation of prohibited concomitant therapy. A copy of the signed ICF (including subject information sheet) will be given to the subject (and IHS-810 form for subjects recruited from US).
- Check selection criteria suitability
- Perform dilated ophthalmoscopy / retinal photography (if it was not done in the last 6 months) to exclude active proliferative retinopathy
- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record demographic details (age, height, gender, and race)
- Record body weight and calculate BMI
- Record medical history, concomitant illnesses and concomitant medications
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate)
- Record detailed history of all previous insulin use
- Perform and document physical examination
- Perform 12-lead ECG (supine, after 5 minutes rest) and document results
- Collect blood and urine samples for the following laboratory assessments:
    - Fasting C-peptide
    - Serum pregnancy test for women of childbearing potential
    - HIV, HBsAg, and HCVAb
    - Hematology
    - Blood chemistry
    - Urine analysis
    - HbA1c
    - Fasting plasma glucose
    - Fasting lipid profile
    - Immunogenicity analysis

For suspected lab errors, 1 repeat of the specific test will be allowed during the 14-day screening period.

After all assessments (except immunogenicity) have been performed, the investigator will assess the results for compliance with the inclusion and exclusion criteria. If all inclusion

criteria have been fulfilled and none of the exclusion criteria were met, the subject may be enrolled into the run-in phase. The run-in visit must be scheduled no later than 14 days after the start of the screening phase (date of subject signature on ICF).

6.2 Run-in Period

6.2.1 Visit 2 (Week -4)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Collect blood sample for fasting plasma glucose
- Dispense subject diary to the subject and provide information regarding the completion requirements and necessary glucose measurements provided.
- Review current dosing of Lantus and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Dispense study medication and provide dose and titration instructions
- Dispense ancillary supplies

6.2.2 Visit 3 (Week -3), Visit 5 (Week -1)

These visits can be performed as telephone contacts if preferred by site and subject. If the visit is performed as a telephone contact, a time and date must be agreed in advance by both parties and the subject must have the completed subject diary available for discussion of the entries during the call.

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of Lantus and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change

6.2.3 Visit 4 (Week -2)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood sample for fasting plasma glucose
- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of Lantus and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided.

6.3 Treatment phase

6.3.1 Visit 6 (Week 0)

After completion of the run-in phase without any major violation of the selection criteria the subjects will enter the randomized study treatment phase. During this visit the following procedures and assessments will be performed:

- Check selection criteria suitability
- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record body weight and calculate BMI
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate)
- Perform and document physical examination
- Perform 12-lead ECG (supine, after 5 minutes rest) and document results
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
    - Serum and urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
    - Fasting plasma glucose
    - HbA1c
    - Hematology
    - Blood chemistry
    - Urine analysis
    - Fasting lipid profile
    - Immunogenicity analysis (collect blood sample prior to study drug administration)
    - PK analysis (collect blood sample prior to study drug administration)

- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of Lantus and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Dispense study medication MYL-1501D (product from Process VI or Process V), and Humalog
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided.
- Perform randomization and document result

6.3.2 Visit 7 (Week 1), Visit 9 (Week 4), Visit 11 (Week 9)

These visits can be performed as telephone contacts if preferred by site and subject. If the visit is performed as a telephone contact, a time and date must be agreed in advance by both parties and the subject must have the completed subject diary available for discussion of the entries during the call.

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change

6.3.3 Visit 8 (Week 2), Visit 10 (Week 6)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
    - Serum and urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
    - Fasting plasma glucose
    - Immunogenicity analysis (collect blood sample prior to study drug administration as outlined in Table 1)

  - PK analysis (collect blood sample prior to study drug administration as outlined in Table 1)
- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided.
- Only applicable to Visit 10, Dispense study medication MYL-1501D (product from Process VI or Process V) and Humalog

6.3.4 Visit 12 (Week 12)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate)
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
  - Serum and urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
  - Fasting plasma glucose
  - HbA1c
  - Fasting lipid profile
  - Immunogenicity analysis (collect blood sample prior to study drug administration as outlined in Table 1)
  - PK analysis (collect blood sample prior to study drug administration as outlined in Table 1)
- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Dispense study medication MYL-1501D (product from Process VI or Process V) and Humalog
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided

6.3.5 Visit 13 (Week 15)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
    - Serum and urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
    - Fasting plasma glucose
- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided

6.3.6 Visit 14/ End of Treatment (Week 18)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record body weight and calculate BMI
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate)
- Perform 12-lead ECG (supine, after 5 minutes rest) and document results
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
    - Serum and urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
    - Fasting plasma glucose
    - HbA1c
    - Hematology
    - Blood chemistry
    - Urine analysis
    - Fasting lipid profile
    - Immunogenicity analysis (collect blood sample prior to study drug administration as outlined in Table 1)
    - PK analysis (collect blood sample prior to study drug administration as outlined in Table 1)
- Review the results of 8-point SMBG measurements, performed on 3 days during the week

- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided

6.3.7 Early study drug Termination (ET) visit

Subjects may request termination of study drug or withdrawal from the study at any time, or be required to withdraw or terminate study drug by the investigator or sponsor for reasons as per Section 4.3.4. If study drug is terminated or the subject withdraws or is withdrawn, the reason for termination/withdrawal should be established and recorded. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the outcome of subject contact attempt, if possible. The investigator will contact Mylan or designee, if subject fails to complete the study or violates the protocol.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Unless consent is withdrawn, subjects who prematurely terminate study drug will be asked to return to the clinic to conduct the ET visit as soon as possible after their last dose of study drug, and in case consent subject will be asked to conduct all the remaining visits according to study schedule table until the end of the study.

At the ET visit the End of Treatment visit (Week 18/Visit 14), procedures should be completed.

The site should explain the importance of data collection and make every effort to consent the subject to continue follow up per the SCHEDULE OF ACTIVITIES until Week 20 visit.

6.4 Visit 15 Follow up (Week 20) (telephone call)

- Record AEs, SAEs, local and systemic allergic reactions and severe hypoglycemic which are classified as SAE.
- Record concomitant medications since previous visit

6.5 Treatment Procedures

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator or designated representative will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator or designated representative will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The Mylan study team will be informed of these incidents in a timely fashion.

Activities specific to this protocol are expanded upon further below.

6.5.1 Blood Volume

Total blood sampling volume for an individual subject is approximately 230 mL.

Table 3: Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Safety Labs	30	1	3	120
PK[1]	4		5	20
Anti-drug antibody (ADA)[2]	10	1	5	60
Supplemental Immunogenicity[3]	10 (baseline), 5 (V1, V8, V10, V12, V14)	1	5	35
TOTAL				**235**

[1] Blood samples (1 x 4 mL) will be drawn into K_2EDTA plasma tubes.
[2] Blood samples (2 x 5 mL) will be drawn into serum separator tubes (SST).
[3] Blood samples (1 x 5 mL; 2 x 5 mL at baseline) will be drawn into serum separator tubes (SST).

6.5.2 Safety Testing Assessments

Safety will be assessed through physical examinations, monitoring of vital signs, 12-lead electrocardiograms, laboratory analyses, and adverse event monitoring.

6.5.2.1 Adverse Event Assessment

If a subject reports any symptoms after the signing of the informed consent form, they will be evaluated by medical staff and necessary measurements will be performed. The Principal Investigator or Medical Sub-Investigator will be notified before dosing to determine the course of action.

Clinically relevant findings from screening procedures, e.g., laboratory tests or physical examinations will be recorded as medical history. Clinically significant changes from the screening procedures results will be recorded as adverse events.

Subjects will be routinely queried with regard to the presence or absence of adverse events using open ended questions. The clinic will provide documentation of any adverse events in the subject's CRF. The adverse event source documentation will minimally include the following information: date and time of assessment, the outcome of the response, and identification of the clinic staff member collecting the information.

6.5.2.2 Hypoglycemia

Incidence of hypoglycemic episodes will also be summarized by category (Severe Hypoglycemia, Documented Symptomatic Hypoglycemia, Asymptomatic Hypoglycemia, Probable Symptomatic Hypoglycemia, Relative Hypoglycemia and Nocturnal Hypoglycemia). In addition, nocturnal hypoglycemia rate and incidence will be analyzed in a same way as overall hypoglycemic episodes.

Hypoglycemia is a state produced by a lower than normal level of glucose in the blood. This may develop, if for example:

- The subject misses or delays meals or there is a change in diet
- The subject takes a higher dose of study drug than prescribed
- The subject consumes alcohol
- The subject does more intense or longer physical exercise or work than normal,
- The subject is recovering from an injury, operation, fever or other illness, or from other forms of stress

6.5.2.2.1 Classification

A. Severe Hypoglycemia

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

B. Documented Symptomatic Hypoglycemia

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

C. Asymptomatic Hypoglycemia

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

D. Probable Symptomatic Hypoglycemia.

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

E. Relative Hypoglycemia.

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

F. Nocturnal Hypoglycemia.

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

Note: A diagnosis of severe hypoglycemia as per above classification will always be considered as serious adverse event. Other hypoglycemic episodes which fulfils ICH criteria for seriousness (life-threatening, hospitalization etc.) or represent important medical events based on investigator's judgment should also be reported to sponsor within 24 hours.

6.5.2.2.2 Identification of Hypoglycemia

Symptoms of hypoglycemia include but are not limited to the following: palpitations, sweating, hunger, nervousness and shakiness, perspiration, dizziness or light–headedness, sleepiness, confusion, difficulty speaking, feeling anxious or weak. Neuroglycopenic manifestations may include seizure, coma, and even death.

Subject will be instructed to be alert for signs and symptoms of hypoglycemia; and if possible to take glucose meter readings at the time of the episode and to record the details of the episode with any remedial action taken and the blood glucose level (if it was checked) in their diary.

Investigators will instruct the subjects on self-management of hypoglycemic episodes. Investigators will also instruct subjects on remedial actions to be taken during the episodes of severe hypoglycemia. Subject will be encouraged to call the study site if they experience hypoglycemia.

6.5.2.2.3 Management of Hypoglycemia

The following steps are recommended for managing hypoglycemic episodes:

1. The subject should begin with 15 to 20 grams carbohydrate (e.g., 3-4 teaspoons of table sugar dissolved in water, 1 tablespoon of honey, ¾ cup of juice or regular soft drink, 3-4 glucose tablets).

2. Subsequently, if the glucose level is ≤50 mg/dL, then the subject will be asked to consume 20 to 30 grams carbohydrate (e.g., 4-6 teaspoons of table sugar dissolved in water, 2 tablespoons of honey, ¾ cup of juice or regular soft drink, 4-5 glucose tablets).

3. Subject will be asked to recheck blood glucose after 15 minutes and to repeat hypoglycemia treatment if the blood glucose does not return to normal after 15 minutes. If the next meal is more than 1 hour away, subjects should follow with additional carbohydrate or a snack.

4. If hypoglycemia persists after the second treatment, subject or companion should be instructed to contact the investigator.

It is recommended that the subjects always carry some sugar lumps, sweets, biscuits, or sugary fruit juice.

For an event of severe hypoglycemia the subject can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate training, or glucose given intravenously by a medical professional. Intravenous glucose can also be given if the subject does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness administration of oral carbohydrate is recommended in order to prevent a relapse.

Full hypoglycemic episode documentation includes time of occurrence, duration, time of recovery, remedial measures undertaken, recording the symptoms and plasma glucose / SMBG levels at the beginning and end of the episode with time and date, and classification in to the different subtypes (Refer to Section 6.5.2.2.1).

6.5.2.2.4 Reporting of hypoglycemic episodes

Hypoglycemic events and any associated symptoms are recorded only on the hypoglycemic episodes page of the CRF. Severe hypoglycemia and those episodes meeting any of the ICH seriousness criteria (Section 9.2.4) are also to be notified as SAEs to the Mylan Global Product Safety and Risk Management department, as described in Section 9.3.2.8; and entered on the SAE and AE pages.

6.5.2.3 Laboratory Safety

The following safety laboratory tests will be performed at times defined in the study schedules in Sections 1 and Section 6.

Table 4: Laboratory Safety Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and Creatinine Glucose Calcium Sodium Potassium Chloride AST, ALT Total Bilirubin Direct/Indirect bilirubin Alkaline phosphatase Uric acid Albumin Total protein CRP C-Peptide Lipid Profile	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy/culture[a]	Urine hCG HIV and HBSAg and HCVAb HbA1c
[a] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.			

Hematology and chemistry will be analyzed by central laboratory. Urinalysis will be conducted by dipstick at site and if urine is positive for blood, protein, nitrites, or leukocyte esterase, will be analyzed via microscopy/culture by a central laboratory.

Blood volumes to be collected and blood and urine sample handling instructions will be provided in the central vendor laboratory manual. The central laboratory will provide collection materials and directions for packaging and shipment of samples.

Any clinically significant findings in laboratory safety data should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.5.2.4 Immunogenicity Assessment

Blood samples of 5 mL each will be taken into serum separator tubes at each time point as outlined in Table 1. At Visits 1, 8, 10, 12, and 14, three blood samples will be drawn, whereas at Visit 6 (baseline) four blood samples will be drawn. The blood samples will be taken by direct venipuncture, and the exact times of blood sampling will be recorded in the CRF. Two of the samples will be used to determine the presence of anti-drug antibodies against insulin glargine using the approach outlined below. The other sample will be collected and stored in reserve for potential supplemental immunogenicity testing and/or

characterization. Samples collected pre-dose at the randomization visit (Visit 6) will be considered as baseline. Samples collected at screening and the supplemental samples collected at baseline may also be used for method development and validation. Sample handling instructions are specified in the laboratory manual.

A conventional radioimmunoprecipitation assay (RIPA) will be employed for the assessment of anti-drug antibodies in clinical samples. In this assay, samples will undergo a pre-treatment step that includes acid dissociation to release any anti-insulin antibodies complexed with free drug, followed by charcoal adsorption of the free insulin analog. The treated samples will be incubated with a fixed amount of ^{125}I-MYL-1501D, and anti-drug antibody complex formation with the tracer is measured via gamma counter and expressed as a percentage of bound to total radioactivity (%B/T).

The multi-tiered sample analysis recommendations for immunogenicity testing from published white papers [7, 8], and current regulatory guidance [9, 10], will be employed for the immunogenicity assessment of MYL-1501D Process V and Process VI. The antidrug antibody analysis methodology will be fully validated, and the sample analysis procedures will be documented in a Sample Analysis Protocol. Sample handling, processing, and storage instructions will be detailed in a separate manual. The laboratory for immunogenicity analysis will be designated by the Sponsor.

6.5.2.4.1 PK Assessment

One blood sample of 4 mL will be taken into a K_2EDTA plasma tube at each time point, as outlined in Table 1. The blood samples will be taken by direct venipuncture, and the exact times of blood sampling will be recorded in the CRF. The PK sample will be taken along with the immunogenicity samples. The exact time of last MYL-1501D dose prior to withdrawal of blood for PK will be noted. The blood samples will be analyzed for Insulin Glargine, Glargine M1 and M2 metabolite concentrations by Covance Laboratories Ltd. (Harrogate, UK) using a fully validated analytical method. Sample handling instructions are specified in the laboratory manual.

The PK samples are taken as outlined in Table 1. The PK sample will be taken during the visit, preferably taken 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.

6.5.2.5 Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Sections 1 and Section 6. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg after 5 minutes of rest. Where possible, the same arm (preferably the dominant arm) will be used throughout the study.

The same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring blood pressure and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. Any clinically significant

changes in blood pressure and pulse rate should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.5.2.6 12-lead ECG

In this study, 12-lead ECGs will be recorded using local ECG devices and review. ECGs should be collected at times specified in the study schedules in Sections 1 and Section 6.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the subjects, a medically qualified individual at the site will assess ECG recordings and make any comparisons to baseline measurements.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. Any clinically significant ECG abnormalities measured at screening should be assessed for their effects on subject eligibility of the study and recorded in medical history. ECG parameters will not be recorded in the CRFs, but any clinical significant changes between the screening and subsequent ECGs should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.5.2.7 General Physical Examination

A full general physical examination will consist of an examination of the abdomen, cardiovascular system, lungs, lymph nodes, musculoskeletal and neurological systems, skin, extremities, head, ears, eyes, nose, and thyroid gland by trained medical personnel at the site. A full physical examination will be performed at Visit 1 (screening), 6 (randomization) and 14 (EOT or ET).

Height and weight will be assessed at Visit 1. Physical examination results will not be recorded in the CRFs, but any clinical significant finding at Screening (Visit 1) should be recorded under medical history and changes between Screening (Visit 1) and subsequent examinations should be recorded as an AE. Determination of clinical significance and seriousness will be based on the investigator's medical judgment.

7 STATISTICAL ANALYSIS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

7.1 Sample Size Determination

A total of 202 subjects with T1DM are planned to be randomized for this study and will receive either MYL-1501D Process V product or MYL-1501D Process VI product, in a 1:1 ratio.

The sample size estimation is based on assumptions for the change from baseline up to week 18 in HbA1C with either MYL-1501D product from Process V or Process VI. It is assumed, that true mean groups mean difference is 0.03 and standard deviation is equal to 0.74. To demonstrate non-inferiority margin of 0.4% using a 2-sided 95% confidence interval and a 90% power, a total of 172 subjects (86 subjects per treatment group) are required.

To account for a maximum of 15% of subjects being not eligible for the per protocol analysis, a total sample size of 202 is planned to be randomized for this study. The true treatment difference and standard deviation is based on previous study MYL-GAIA-3001.

No replacement of subject will be performed if subject discontinued prematurely from the study.

7.2 Primary Endpoints

7.2.1 Definition of Primary Endpoints

The change in HbA1c from baseline up to week 18 is the primary endpoint for this study.

7.2.2 Statistical Methodology for Primary Endpoints

For the analysis of the primary endpoint all subjects will be taken account – irrespectively of their missing value pattern, which are expected to be limited to less than 5% of the subjects. Then the treatment effect will be estimated using a repeated measures analysis employing a restricted maximum likelihood (REML)-based, mixed model repeated measures (MMRM)-effects model approach. In this model all subjects will be used for the estimation of the 95% confidence interval of the difference between MYL-1501D Process VI product and Process V product for mean change in HbA1c at week 18. The MMRM model will include the fixed, categorical effect of treatment group assignment, visit, treatment group-by-visit interaction and the other fixed effect terms investigator, basal insulin dose time, and baseline HbA1c value as covariates.

Further details on the MMRM model will be provided in the SAP. Investigator pooling will be finalized before unblinding treatment to avoid introducing bias. The detailed method of investigator pooling will be documented in the SAP.

7.2.3 Primary Analysis for Primary Endpoints

For primary endpoint analysis, non-inferiority for efficacy will be established if the upper limit of a two sided 95% confidence interval for the absolute difference (MYL-1501D Process VI minus Process V) of mean change from baseline to endpoint for HbA1c is no greater than 0.4% at Week 18. The primary analysis will be performed on the intent to treat (ITT) analysis set.

7.2.4 Secondary/Sensitivity Analyses for Primary Endpoints

A further robustness check will be conducted using the PP population and applying the same MMRM procedure as described in previous section to establish non-inferiority. Any differences in the conclusion will be further investigated by examining differences between the ITT and the PP populations.

Other sensitivity analysis addressing missing data will be conducted in the following manner:

Multiple imputed datasets will be generated based on the assumption of a monotone missing data pattern. The imputation will be performed using the monotone regression method for week 12 and week 18 sequentially. The variables treatment, pooled investigator, and basal insulin dose time will be used as independent.

In a second step, the imputed values will be corrected such that the full non-inferiority margin will be added for imputed values in Process VI group. All imputed datasets will be analyzed using the same model parameters as used in the primary analysis, and the results will be combined using Rubin's rules.

A standard last observation carried forward (LOCF) approach will be conducted such that missing data will be imputed by LOCF. This dataset will be analyzed for the ITT and PP populations using the ANCOVA model described in the protocol.

7.2.5 Missing Data

The only imputed data will be performed in the sensitivity analysis as described above for HbA1c. Otherwise, missing data will not be imputed.

7.2.6 Sub-Group Analyses

Subgroup analyses of important factors, including but not limited to factors such as age group, gender and race are planned for the key outcomes of HbA1c and immunogenicity variables. These will be conducted by adding factor and treatment-by-factor interactions to the MMRM model models of the main analyses. Other exploratory subgroup analyses may be performed, as deemed appropriate.

7.3 Secondary Endpoints

The following efficacy measures (both actual and change values) will be summarized at baseline and scheduled visit. Similar statistical analysis approach for primary will be performed for continuous variables. Contrasts of LS mean at each scheduled visit will be used to evaluate all pairwise treatment comparisons, and 95% confidence intervals for treatment differences in LS means will be computed for each visit.

- Change in fasting plasma glucose from baseline
- Change in basal insulin, meal-time, and total insulin dose per unit body weight (U/kg) from baseline
- Change in 8-point SMBG profile from baseline.

All above analyses will be performed on ITT set.

The following safety measures (both actual and change values) will be summarized at baseline and scheduled visit. Contrasts of LS mean at each scheduled visit will be used to evaluate all pairwise treatment comparisons, and 95% confidence intervals for treatment differences in LS means will be computed for each visit. For categorical data analyses, Fisher's exact test or Chi-squared test will be used. The details will be provided in the SAP.

- Incidence of positive antibody response and change in antibody percentage binding from baseline.
- Change in hypoglycemia rate (30 day adjusted) from baseline and incidence of hypoglycemic events
- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Incidence of local allergic reactions, systemic allergic reactions and other adverse events
- Incidence of device-related safety assessment

The incidence of subjects with each of the three following criteria will be summarized descriptively (for categorical measures) by treatment to explore possible insulin neutralization effect:

- An increase of over 10% in cross reacting antibodies from baseline
- Increases in HbA1c of over 0.2% from baseline at any visit
- Increase in total or basal insulin dose at any visit

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

All above analyses will be performed on safety set.

7.4 Analysis Set Definitions

The ITT analysis set includes all randomized subjects (including subjects who receive incorrect treatment, do not complete the study or do not comply with the protocol or used prohibited medication) and have baseline (randomization visit) and at least one post-baseline efficacy value.

The PP analysis set includes subjects who complete Week 18, and have HbA1c measurements as per the protocol, or have at least one post-baseline HbA1c data (for subjects

who discontinue prematurely); and do not have protocol violations that impact the primary outcome (as detailed in the statistical analysis plan). Subjects who meet rescue medication criteria and take rescue medication will be excluded from PP analysis set. The subjects excluded from the PP population will be identified before database lock (i.e., before unblinding the study team).

The safety analysis set includes subjects who take at least one dose of the study medication after randomization. For safety analyses, subjects will be categorized according to the treatment that they actually received.

7.5 Other Safety Analyses

The analysis set for safety summaries is defined as all subjects who received at least one dose of study medication in the randomized treatment period. Safety data from the run-in period will be presented in listings only.

Treatment emergent adverse events and concomitant medications will be summarized and listed. All AEs that occur after the first dose of double-blind study medication through 14 days after the last dose will be considered treatment emergent AEs. The number and percentage of subjects with at least one treatment emergent AE will be presented by treatment group and events further summarized by maximum severity and relationship to study medication.

Descriptive statistics will be provided for the following safety data. No inferential analysis of this safety data is planned. Any ECG, blood pressure, and pulse rate abnormalities of potential clinical concern will be described.

7.5.1 Vital Signs

Change from baseline of vital sign measurements will be analyzed using MMRM with model terms of pooled investigator, basal insulin dose time, treatment, visit, treatment-by-interaction as fixed effects, and baseline value as covariate. The descriptive statistics including actual measurement and change from baseline along with treatment comparison will be performed at scheduled visits.

The percentage of subjects in categories such as potentially clinically significant will be summarized and treatment comparison will be performed using Fisher's exact test.

7.5.2 ECG Analyses

The percentage of subjects in categories such as abnormal/non-clinically significant and abnormal/clinically significant will be summarized and treatment comparison will be performed using Fisher's exact test.

7.5.3 Laboratory Data

Change from baseline of laboratory measurements will be analyzed using MMRM with model terms of pooled investigator, basal insulin dose time, treatment, visit, treatment-by-visit interaction as fixed effects, and baseline value as covariate. The descriptive statistics for actual measurement and change from baseline along with treatment comparison will be performed at scheduled visits.

The percentage of subjects in categories such as abnormal/non-clinically significant and abnormal/clinically significant will be analyzed using Fisher's exact test. P-value for the two-sided test will be presented.

8 ADMINISTRATIVE PROCEDURES

8.1 Source Documentation Forms

All clinical data will be recorded by the clinical staff on raw data sheets and/or recorded electronically using validated software. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidance.

The nature and location of all source documents will be documented separately. Source data may be directly captured from devices, transferred from 3rd parties (e.g. laboratory data) or entered manually into CRF/database.

8.2 Access to Data/Source Documentation

The Investigator or designated representative will permit full access to data and source documentation for the purpose of clinical monitoring, audits, IRB/IEC review and regulatory inspections.

8.3 Final Clinical Study Report and Case Report Forms (CRFs)

A written clinical study report will be provided in accordance with the International Conference on Harmonization (ICH) E-3 guidelines including Annex I (Synopsis) documenting the clinical execution of the study. This report will include a description of any protocol deviations. The final report will also include reasons for withdrawals and any necessary treatment(s). The report will also include tables presenting demographics (separate summary tables for enrolled and completed subjects), and adverse events recorded during the study. In addition, the clinical study report will include a Quality Assurance statement, documenting that the report has been reviewed for completeness, accuracy, and compliance with the protocol and applicable local and federal regulations. For final clinical reporting purposes only, adverse events deemed “definite”, “probable” or “possible” will be included in the treatment-related summaries/listings.

Case Report Forms containing data transcribed from subject source documents (as appropriate) and copies of other source documents will be supplied by the clinical site. The Principal Investigator must sign each subject’s CRF after completion of data entry, signifying that the data entered in the CRF is complete and accurate. Electronic CRFs may be provided.

8.4 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well-being of the study subjects requires medical treatment, the study will be conducted as described in the approved protocol (and amendments, if applicable), GCP and applicable SOPs. In addition, the study will be conducted in accordance with the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted. Any deviation(s) from the protocol will be recorded and presented in the final report.

8.5 Data Handling and Record Retention

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the study subjects remains protected.

A CRF is required to be completed for each subject receiving study medication. The CRF is property of the sponsor and the Investigator must review all CRFs prior to submission to the sponsor.

The CRF may be consider as the source document, the investigator must seek prospective agreement to the sponsor in writing to use the CRF as source document prior the start of the study. In addition, items directly recorded in the CRF must be documented that they will be considered as source.

All records pertaining to the receipt and return of study supplies (particularly study medication) and copies of final case report forms, worksheets, and other pertinent source documents must be retained in accordance with ICH-GCP and the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

The investigator must obtain in writing the sponsor's agreement to dispose of any records, even if the retention period has been reached.

8.6 Confidentiality

Information furnished to Clinical Investigators and IRBs/Ethics Committees will be maintained in confidence by the Clinical Investigator and IRB/Ethics Committee. By signing this protocol, the Investigator affirms to the Sponsor that he/she will maintain, in confidence, information furnished to the IRB/Ethics Committee relevant to this study under appropriate understanding of confidentiality with such IRB/Ethics Committee.

By signing the protocol, the Investigator agrees that within local regulatory restrictions and institutional and ethical considerations, the Sponsor may consult and/or copy source documents (e.g., laboratory/X-ray reports, ECG tracings, workbooks, medical records) in order to verify CRF data.

8.7 Ethics and Regulatory Authorities

Guidelines will be followed with regard to the treatment of human subjects in the study, in accordance with the requirements of the Declaration of Helsinki and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E6) in addition to the regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

8.7.1 Institutional Review Board/Ethics Committee

The Investigator is responsible for obtaining initial and continuing review (at intervals not more than once per year) of the study by an IRB/Ethics Committee, or in accordance with applicable government regulations of the country where the study is being conducted as well as the country where the study will be submitted. This study will not enroll any subjects until the IRB/Ethics Committee provides written approval of the protocol and the informed

consent to the investigator. In addition, a copy of the IRB/Ethics Committee approval documents must be provided to the sponsor prior to enrolling any subjects into the study.

8.7.2 Regulatory Authority

This clinical study protocol, title and a list of investigational sites, IEC(s)/IRB(s) approvals, as well as other relevant documentation will be submitted to the local Regulatory Authorities for review and approval prior to study start. Upon completion, the Regulatory Authorities will be notified the study has ended. The study will only be undertaken in compliance with the local regulatory requirements.

8.8 Informed Consent

A properly executed, written informed consent in compliance with current GCP guidelines and ICH guidelines shall be obtained from each volunteer prior to entering the study. A copy of the informed consent document to be used will be submitted by the investigator to an independent institutional review board (e.g. IRB or ethics committee) and the Sponsor and/or its agent for review and approval prior to the start of the study. The investigator shall provide a copy of the signed and dated informed consent to the subject, and a signed and dated copy shall be maintained in the volunteer's medical record.

8.9 Disclosure and Publication of Clinical Study Data

The disclosure and publication of clinical study data will be detailed in the clinical study agreement with the Investigators.

8.10 End of Study

The end of study is considered to be the date of last subject last visit or the date of early termination of the study whichever is the later.

9 ADVERSE EVENT REPORTING

9.1 Adverse events

All observed or subject-reported AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as outlined in this section.

The Investigator must pursue and obtain information adequate both to determine the outcome of all AEs and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Mylan. The Investigator is required to assess causality and should obtain sufficient information to determine the causality of all AEs. All AEs will be followed until the event is resolved, deemed to be stable, or until the event is found to be due to another known cause (concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted with the sponsor concurring with that assessment.

9.2 Definitions

9.2.1 Adverse Events

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 will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition.

An AE will be defined as a TEAE if the first onset (or worsening, in the case of pre-existing disease) is after the first administration of MYL-1501D after randomization through follow-up visit or 14 days after last dose [for subjects that do not have a follow-up visit].

9.2.2 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose 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 study drug reported as “possible”, “probable” or “definite” will be considered ADRs. If the relationship to the study drug is not given, then the AE must be treated as if the relationship were “possible.”

9.2.3 Unexpected Adverse Event/Adverse Drug Reaction

An unexpected AE or ADR is defined as one whose nature or severity is not consistent with the applicable reference safety information designated for the study. For example, hepatic

necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

The reference safety document for MYL-1501D is the IB. For Humalog® and any concomitant medication, the respective SmPC or US prescribing information will be the reference safety document.

9.2.4 Serious Adverse Events

A SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
    - NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly.
    - NOTE: A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is considered an SAE. However, a newly diagnosed pregnancy in a patient that has received the study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy. The patient with newly diagnosed pregnancy will discontinue receiving study treatment and will be followed-up every 3 months until delivery or termination to gather information about the outcome of the pregnancy.
- Is an important medical event.
    - NOTE: Important Medical Event: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and / or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
    - For this protocol, any cancer, including localized basal cell carcinoma, is considered an important medical event, to be reported as a SAE.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
    - NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. Events NOT to be reported as SAEs are hospitalizations for the following:
        - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
        - Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.
        - Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care).

- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Hospitalization also does not include the following:

- Rehabilitation facilities.
- Hospice facilities.
- Respite care (e.g., caregiver relief).
- Skilled nursing facilities.
- Nursing homes.

Any non-serious AE that is determined by the medical monitor/sponsor to be serious (per company policy or regulatory requirements) will be communicated to the Investigator for reclassification. To assist in the determination of case seriousness further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

9.3 Management of Adverse Events

AEs or SAEs will be collected from the time the subject signs the informed consent form until the follow-up visit or 14 days after last dose of study medication. Pre-existing diseases or conditions (reported at visit 1 in medical history) will not be considered as AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition. An SAE deemed to be related to the study drug by the Investigator in consultation with sponsor will be reported even after the Follow-up visit if reported by subjects.

9.3.1 Collection

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The Investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as

- “How are you feeling?”
- “Have you experienced any issues since your last visit?”
- “Have you taken any new medications since your last visit?”

Any clinically relevant observations made by the Investigator during the visit will also be considered AEs.

The Subject’s diary should also be reviewed at each study visit for adverse events. At week 0 visit when study diaries are issued, subjects will be appropriately educated by the study designee on what constitutes an adverse event and instructed to record adverse events in the study diary in a timely manner.

9.3.2 Evaluation

9.3.2.1 Severity Assessment of Adverse Events

The clinical severity of an AE will be graded using the NCI-CTCAE Criteria Version 4.03. A copy of these criteria will be provided to each study site. If an AE is not listed in the CTCAE, its clinical severity will be classified as follows:

Table 5: Clinical Severity of Adverse Events

The Investigator will use the terms defined below to describe the maximum intensity of the AE.	
Grade 1 – MILD	Does not interfere with subject's usual function.
Grade 2 – MODERATE	Interferes to some extent with subject's usual function.
Grade 3 – SEVERE	Interferes significantly with subject's usual function.
Grade 4 - LIFE-THREATENING	Risk of death at time of event
Grade 5 – DEATH	Death related to AE

If an AE is graded 4 or 5 according to the above criteria, then the AE meets the criteria for an SAE and the Investigator should immediately notify the sponsor or designee as described in Section 9.3.2.8.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity based on the CTCAE grading or on the above table, whereas an SAE is an AE that meets any of the regulatory specified criteria required for designation as seriousness described in Section 9.2.4.

9.3.2.2 Action Taken

The possible actions taken for an AE are described in Table 6.

Table 6: Action Taken for an Adverse Event

Dose reduced	The dose regimen was reduced by changing its frequency, strength, or amount.
Dose increased	The dose regimen was increased by changing its frequency, strength, or amount.
Treatment interrupted	The treatment was temporarily interrupted.
Treatment withdrawn	The treatment was permanently discontinued.
Concomitant therapy or procedures	Treatment was needed as a result of the AE (the concomitant treatment should be recorded on the relevant page of the CRF).
Unknown	Not known, not observed, not recorded, or refused.
No action taken	The AE did not require any intervention.
Not applicable	AE occurred after study medication was permanently withdrawn or subject completed the treatment period.

9.3.2.3 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

All ongoing AEs without fatal outcome (i.e. did not cause death) will be recorded as not recovered/not resolved at the time of death.

*Only select fatal as an outcome when the AE results in death. If more than one AE is possibly related to the subject's death, the outcome of death should be indicated for the AE which is the most plausible cause of death in the opinion of the Investigator.

Note: although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

9.3.2.4 Causality Assessment of Adverse Events

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. The Investigator must make an assessment of the relationship of each AE (serious and non-serious) to the study treatment(s) and record this relationship in the CRF.

In addition, if the Investigator determines an AE or SAE is associated with study procedures, the Investigator must record this information about the causal relationship in the source documents and CRF, as appropriate, and report the assessment in accordance with the reporting requirements, as applicable, AE or SAE.

Factors that need to be considered when making a causality assessment include:

- Temporal relationship (e.g., time of onset)
- Clinical and pathological characteristics of the event(s)
- Pharmacological plausibility
- Exclusion of confounding factors (medical and medication history)
- Drug Interactions
- De-challenge/re-challenge
- Dose relationship

A suspected relationship (definite, probable, and possible) between the events and the study medication means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality. The Investigator is responsible for assessing relationship of AEs to study treatment in accordance with the following definitions:

Table 7: Definition of Suspected Relationship between the Events and Study Medication

DEFINITELY	Causal relationship is certain	For Example: the temporal relationship between drug exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLY	High degree of certainty for causal relationship	For Example: the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other

		causes have been eliminated or are unlikely.
POSSIBLY	Causal relationship is uncertain	For Example: the temporal relationship between drug exposure and the AE onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal, and while other potential causes may or may not exist, a causal relationship to study drug does not appear probable
UNLIKELY	Not reasonably related although a causal relationship cannot be ruled out	For Example: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible), or disease or other drugs provide plausible explanations
UNRELATED/NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible

For SAEs, the relationship to the study treatment(s) is considered to be unlikely or not related/unrelated, an alternative suspected etiology should preferably be provided (e.g., concomitant medications, intercurrent condition) wherever applicable and available.

9.3.2.5 Documentation

All AEs occurring within the period of observation for the study must be documented in the CRF with the following information; where appropriate (the period of observation for the study is described in Section 6):

- AE name or term in standard medical terminology.
- When the AE first occurred (start date and time); SAE start date is defined as the date the AE became serious.
- When the AE stopped (stop date and time or date and time of last observation if ongoing, i.e., recovering or not recovered).
- Severity of the AE.
- Seriousness criteria (hospitalization, death, etc.).
- Action taken with study medication as a result of AE.
- Outcome.
- Investigator's opinion regarding the AE relationship to the study treatments.

Hypoglycemic events and associated signs/symptoms will only be recorded on the hypoglycemic episodes page of the CRF, unless they are SAEs (i.e., a severe episode).

9.3.2.6 Treatment of Adverse Events

AEs that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the reason should be documented in the CRF; this can include temporary interruption of study treatment. The decision about whether the subject may resume the study treatment will be made by the sponsor after consultation with the Investigator and/or medical monitor.

9.3.2.7 Follow-up

Any AE will be followed-up to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate CRF page.

9.3.2.8 Notification

For SAEs, the active reporting period to Mylan, begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including the follow up visit. Should an Investigator be made aware of any SAE occurring any time after the active reporting period, the SAE must be promptly reported to Mylan only in case of reasonable causality (i.e. suspected ADR).

The SAE reporting form is to be completed for all serious adverse events, signed by the Investigator, and emailed or faxed with supporting documentation (e.g., CRFs, hospital records, laboratory reports). Subject identity details (such as but not limited to name or clinic/hospital number) must not be visible on SAE forms or any supporting documentation provided by the Investigator. These should be "blacked out", and replaced with the site and subject's study identification number on every page.

At that time of first notification, the Investigator/designee should provide the following information via the SAE report form:

- Protocol number
- Reporter (study site and Investigator)
- Subject's unique identification number
- Subject's age
- Investigational medicinal product
- Date of first dose of study treatment
- Date of last dose of study treatment, if applicable
- SAE term
- The seriousness criteria that were met
- Investigator's opinion of the relationship to the study treatment
- Severity
- Start and stop (if applicable) of the event (date and time)
- A brief description of the event, outcome to date, and any actions taken
- Concomitant medication at onset of the event
- Relevant past history information
- Relevant laboratory test findings

If the initial notification of an SAE is by telephone, within 24 hours of the initial telephone notification the Investigator must email the written SAE report form that describes the SAE to the Mylan Product Safety and Risk Management department.

The Investigator may be requested by Mylan to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Mylan.

Any missing or additional relevant information concerning the SAE should be provided on a follow-up SAE Report Form. Ensure that any additional information requested by the sponsor or designee about the event, as outlined above (e.g., hospital reports, autopsy report) is provided to the sponsor as soon as it is available.

Sponsor Contact Information for Immediately Reportable Events

All SAEs must be notified within 24 hours by email (preferred) or fax to:

Mylan Product Safety & Risk Management

PV MAIL HUB FOR IMMEDIATE SAFETY REPORTS:

pvclinical@mylan.com

In the event that an electronic acknowledgment is not received within 24 hours for a SAE report submitted by email, please forward the report via fax to +1.304.285.6409.

9.3.2.9 Regulatory Reporting

All AEs, including suspected serious unexpected AEs will be reported in accordance with applicable local regulations. The Investigator is required to comply with applicable regulations (including local law and guidance) regarding notification to her/his regulatory authorities, ethics committees (ECs) and institutions.

Suspected unexpected serious adverse reactions (SUSARs), SAEs and other cases required by the concerned competent authorities will be reported by the sponsor or the sponsor's representative to all concerned parties within the prescribed timeframe. The sponsor or representative will also submit periodic safety reports (for e.g., Development Safety Update Reports) as required by international regulations.

9.4 Special Situations

The Investigator should report any case of pregnancy within 24 hours via the pregnancy report form. Pregnancy exposures must be followed until a final outcome is determined (e.g., parturition, spontaneous or scheduled termination).

9.4.1 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the Investigator immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted throughout the study, as detailed in the schedule of assessments. A woman who is found to be pregnant at the randomization visit (Visit 6 [Week 0]), will be excluded from the study. A woman who becomes pregnant during the study will be immediately discontinued from study treatment. Early discontinuation visit assessments should be performed as soon as possible after learning of the pregnancy. This information should be captured in the pregnancy form and reported to Mylan Product Safety and Risk Management within 24 hours from the time of initial knowledge, even if beyond the closure of the clinical database.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or an SAE. A spontaneous abortion is always considered to be a SAE and will be reported to the sponsor within 24 hours of knowledge of the event.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered to be an elective procedure and not an AE, nevertheless, Mylan requests that the outcome (e.g., elective termination) be reported within 24 hours and sent as a follow-up on the Delivery and Infant Follow-up Form).

The Investigator is also responsible for following up the pregnancy at 3 monthly intervals until delivery or termination, informing the sponsor about its outcome.

9.4.2 Overdose, Medication Errors and Other Events

Overdose *per se* of either study treatment or a concomitant medication will not be reported as an AE; unless it is an intentional overdose taken with possible suicidal/self-harming intent. Signs, symptoms, and clinical sequelae associated with intentional overdose are to be recorded on the AE CRF page. Dosing and other medication errors are to be recorded as protocol deviations.

9.5 Abnormal Test Findings

Abnormal laboratory findings per se (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., ECG, X-rays, and vital signs) are not reported as AEs. However, abnormal findings that are deemed **clinically significant** or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as an SAE if they meet the criteria of being serious). Clinically significant abnormal laboratory or other abnormal findings that are detected after study drug administration or that are present at baseline and worsen following the administration of study drug are included as AEs (and SAEs, if serious). The Investigator should exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Broad guidance for determining whether an abnormal objective test finding should be reported as an AE follows:

- The test result is associated with accompanying symptoms and/or
- The test result requires additional diagnostic testing or medical/surgical intervention and/or
- The test result leads to a change in study dosing or discontinuation from the study, additional concomitant drug treatment, or other therapy; and/or
- The test result is considered to be an AE by the Investigator or sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE.

Any abnormal test result determined by retest to be an error does not require reporting as an AE.

10 REFERENCE LIST

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MYL-1501D-3004 CLINICAL STUDY PROTOCOL

Protocol Title	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
Product	MYL-1501D (Mylan's Insulin Glargine)
Protocol No.	MYL-1501D-3004
Study Type	Phase 3
Version	2.0
Protocol Date	11 JAN 2018
IND No.	IND 105279
Sponsor	Mylan GmbH Thurgauerstrasse, 40 CH 8050 Zürich, Switzerland

SIGNATURE PAGE

Protocol Description	MYL-1501D-3004
Product Code	MYL-1501D
Protocol Version	2.0
Protocol Version Date	11 JAN 2018

I have read this protocol and affirm that the information contained herein is complete and accurate.

Date: 17 JAN 2018

Global Lead, Safety Surveillance & Risk Management
Dr. Dhaval Panchal, MD

Date: 17th Jan 2018

Senior Director, Biometrics
Dr. Hans-Friedrich Koch, PhD

Date: 17-Jan-2018

Director, Global Clinical Operations
Keri Vaughan

Date: 15 JAN 2018

Global Clinical Director
Dr. Yaron Raiter, MD

Date: 23-JAN-2018

Head, Global Clinical Research and Development
Dr. Abhijit Barve, MD, PhD

DOCUMENT HISTORY

Document Version, Date	Summary of Changes
Final, 18 SEP2017	N/A
Version 2.0 11 JAN 2018	• Titration committee added to guide the dosing of MYL-1501D during treatment period and Lantus® during run-in period (Section 2.2) • Added option of being on stable dose for Levemir® or Toujeo® for at least 3 months at screening (Previously only Lantus was allowed as the only treatment option) (Section 4.2.1) • Updated the Email ID for reporting medication/device related complaints from MGRG.study.medication.complaints@mylan.co.uk to Clinicalbiologicscomplaints@mylan.com (Section 5.2) • ECGs: Updated the requirement for being in supine position from 10 mins to 5 mins prior to an ECG. (Section 6.5.2.6) • Review of results of the 8-point SMBG measurements removed from Visit 7 (Week 1), Visit 8 (Week 2), Visit 9 (Week 4) and Visit 11 (Week 9) (Section 6.3) • Removed fasting Plasma glucose assessment at Visit 13 (Week 15) (Section 6.3) • Primary analysis to include all available outcome data from all randomized patients regardless of treatment discontinuation and use multiple imputation approach for missing data that more appropriately takes treatment adherence into account. (Section 7.2.2, Section 7.2.4 and Section 7.3) • Primary efficacy population (ITT) to include all randomized subjects – irrespective of whether subjects having post-baseline measurement (Section 7.4) • Clarifications and editorial corrections to synchronize text across sections throughout the document

PROTOCOL SYNOPSIS

Protocol Title	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
Background and Rationale	MYL-1501D is being developed as a follow-on biologic to the reference product Lantus® (insulin glargine). A phase 1 PK/PD study comparing MYL-1501D with Lantus® sourced from Europe and U.S. demonstrated PK and PD equivalence between the 3 products. PK/PD equivalence was also demonstrated with MYL-1501D product produced using two manufacturing processes (Process V and Process VI). The aim of this study is to demonstrate similar efficacy and safety between MYL-1501D products produced from two manufacturing processes (Process V and Process VI) in combination with insulin lispro in patients with type 1 diabetes mellitus (T1DM).
Primary Objectives	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 change in HbA1c from baseline to week 18 when administered in combination with mealtime insulin lispro.
Primary endpoints	The primary efficacy endpoint is change in HbA1c from baseline to week 18 for the ITT analysis set.
Methodology and treatments	This is a multicenter, double-blind, randomized, parallel-group phase 3 study in subjects with T1DM comparing the efficacy, immunogenicity and safety of MYL-1501D products from two manufacturing processes (Process V and Process VI). After up to 2-week screening period, all subjects will be titrated on Lantus® during a 4-week run-in period, and will be shifted from their current mealtime insulin to insulin lispro (Humalog®). The subjects will be randomized (stratified by 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 study will be conducted in the US. Approximately 110 sites will be included in the study.
Inclusion/ exclusion criteria	**Inclusion criteria** 1. Written and signed informed consent needs to be provided by subjects or their legal representatives before starting any protocol-specific procedures. 2. Male and female subjects between the ages of 18 to 65 years, both ages inclusive. 3. Subjects with an established diagnosis of T1DM per ADA 2017 criteria who also fulfil the following criteria: a. Initiation of insulin treatment within 6 months of T1DM

diagnosis

b. Treatment with basal-bolus insulin therapy for at least 1 year before screening
c. Fasting plasma C-peptide <0.3 nmol/L (0.9 ng/mL) at screening
d. Subject has been on once daily Lantus® or once daily Levemir® or once daily Toujeo® at stable dose (±15% variation in dose) for at least 3 months at screening

4. Body mass index (BMI) of 18.5 to 35 kg/m^2 at screening (both values inclusive).
5. Stable weight, with no more than 5 kg gain or loss in the 3 months prior to screening, this information will be collected by subject interview during medical history.
6. Glycosylated hemoglobin (HbA1c) ≤ 9.5% at screening.
7. Hemoglobin ≥9.0 g/dL at screening.
8. Subject has the capability of communicating appropriately with the investigator.
9. Subject is able and willing to comply with the requirements of the study protocol including the 8-point self-monitored blood glucose (SMBG), completion of subject diary records and following a recommended diet and exercise plan for the entire duration of the study.
10. Female subjects of childbearing potential who are willing to use oral contraception or acceptable methods of contraception, (e.g., intra-uterine device, spermicidal gel plus condom, diaphragm plus condom, etc.), from the time of screening and for the duration of the study, through study completion.
    a. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    b. Postmenopausal females must have had no regular menstrual bleeding for at least 1 year prior to screening.
    c. Female subjects who report surgical sterilization must have had the procedure at least 6 months prior to screening.
    d. All female subjects of childbearing potential must have negative pregnancy test results at screening and at clinic visits, as per the SCHEDULE OF ACTIVITIES (SOA).
    e. If female subjects have male partners who have undergone vasectomy, the vasectomy must have occurred more than 6 months prior to screening

Exclusion Criteria

1. History or presence of a medical condition or disease that in the investigator's opinion would place the subject at an unacceptable risk from study participation.
2. History of hypersensitivity to any of the active or inactive ingredients of the insulin/insulin analogue preparations used in the study, OR history of significant allergic drug reactions.
3. History of use of animal insulin within the last 3 years or use of approved biosimilar insulin glargine at any time prior to study entry, except for subject who previously participated in MYL-1501D studies and were compliant with the study protocols.

	4. History of use of a regular immunomodulator therapy in the 1 year prior to screening. 5. History of autoimmune disorders other than T1DM or insufficiently treated autoimmune thyroid disorders judged clinically relevant by the investigator (recorded while collecting subject history). 6. History of ≥1 episodes of diabetic ketoacidosis or emergency room visits for uncontrolled diabetes leading to hospitalization within the 6 months prior to screening. 7. History of clinically significant acute bacterial, viral or fungal systemic infections in the last 4 weeks prior to screening (recorded while collecting subject history). 8. Any clinically significant abnormality in electrocardiogram (ECG) or safety laboratory tests (LFT, RFT, hematology or any other laboratory deemed clinically relevant by the investigator) conducted at screening and considered by the investigator to make the subject ineligible for the study. 9. Serological evidence of human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (HCVAb) at screening. 10. History of drug or alcohol dependence or abuse during the 1 year prior to screening. 11. Receipt of another investigational drug in the 3 months prior to screening (or as per local regulations), or if the screening visit is within 5 half-lives of another investigational drug received (whichever is longer), or scheduled to receive another investigational drug during the current study period. 12. Subjects with the following secondary complications of diabetes: a. Active proliferative retinopathy as confirmed by a dilated ophthalmoscopy examination / retinal photography (performed by a person legally authorized to do so) within the 6 months prior to screening. b. Clinical nephrotic syndrome or diabetic nephropathy with a serum creatinine level >1.5 times of upper limit of reference range at screening c. History of severe form of neuropathy or cardiac autonomic neuropathy, recorded while collecting subject history. Subject's with mild or moderate forms of neuropathy will be allowed. d. Subjects with a history of limb amputation as a complication of diabetes (at any time), or any vascular procedure during the 1 year prior to screening. e. History of diabetic foot or diabetic ulcers in the 1 year prior to screening. 13. Any elective surgery requiring hospitalization planned during the study period. 14. Clinically significant major organ disorder at the time of screening including:

a. Uncontrolled hypertension, defined as stage 2 hypertension by Joint National Committee VII (even if therapy is ongoing, blood pressure ≥160 mm Hg systolic or ≥100 mm Hg diastolic).

b. Uncontrolled hyperlipidemia (even if therapy is ongoing, LDL >160 mg/dL or triglycerides >500 mg/dL).

c. Uncontrolled hyperthyroidism or hypothyroidism (subjects can be included if these conditions are controlled with thyroid hormones or anti-thyroid drugs).

d. Impaired hepatic function (alanine transaminase [ALT] or aspartate transaminase [AST] value >2 times the upper limit of the reference range and/or serum bilirubin 1.5 times the upper limit of the reference range at the screening visit). Subjects with evidence of Gilberts disease may be included in the study if they have total bilirubin of <3 mg/dL with indirect bilirubin contributing to >80% of the total bilirubin.

15. History of a significant medical condition, such as:

    a. Clinically significant cardiac disease like unstable angina, myocardial infarction, grade 3 or 4 congestive heart failure (CHF) according to New York Heart Association criteria, valvular heart disease, cardiac arrhythmia requiring treatment, and pulmonary hypertension; during the year prior to screening.

    b. Stroke or transient ischemic attack (TIA) in the 6 months before screening.

16. Subjects with major depressive illness in the last 3 years (those who have well-controlled depression for 3 months on a stable dose of antidepressants, with no major depressive episodes in the last 3 years, can be included, even if they are on medication), subjects with history of other severe psychiatric diseases (manic depressive psychosis [MDP], schizophrenia), which in the opinion of the investigator precludes the subject from participating in the study (recorded while collecting subject history).

17. History of hematological disorders that can affect the reliability of HbA1c estimation (hemoglobinopathies, hemolytic anemia, sickle cell anemia, etc.).

18. Subjects using the following in the 3 months prior to screening:

    a. Insulin pump therapy

    b. Any anti-diabetic drugs other than the study insulins allowed by the protocol.

19. Moderate insulin resistance, defined as requiring insulin of ≥1.5 U/kg/day.

20. Subjects who have received ≥14 consecutive days of glucocorticoid therapy by oral, intravenous, inhaled or other routes that produce systemic effects within the past 1 year, or who have received steroids by any route (except intra-nasal, intra-ocular, and topical) within the 4 weeks immediately preceding screening.

	21. Subjects diagnosed as having cancer (subjects with history of basal cell carcinoma, carcinoma in situ or squamous cell cancer of skin, or in remission >5 years, will be allowed). 22. Subjects who have donated blood or plasma in the 1 month prior to screening
Sample size	A total of 202 subjects with T1DM are planned to be randomized for this study and will receive either MYL-1501D Process V product or MYL-1501D Process VI product, in a 1:1 ratio. The sample size estimation is based on assumptions for the change from baseline up to week 18 in HbA1C with either MYL-1501D product from Process V or Process VI. It is assumed, that true mean groups mean difference is 0.03 and standard deviation is equal to 0.74. To demonstrate non-inferiority margin of 0.4% using a 2-sided 95% confidence interval and a 90% power, a total of 172 subjects (86 subjects per treatment group) are required. To account for a maximum of 15% of subjects being not eligible for the per protocol analysis, a total sample size of 202 is planned to be randomized for this study. The true treatment difference and standard deviation is based on previous study MYL-GAIA-3001.
Statistical Methods	A repeated measures analysis employing a restricted maximum likelihood (REML)-based, mixed model repeated measures (MMRM)-effects model approach will be used to estimate a 95% confidence interval for the absolute difference between MYL-1501D Process V product and MYL-1501D Process VI product for mean change in HbA1c at Week 18. Non-inferiority for primary objective will be established if the upper limit of a two sided 95% confidence interval for the absolute difference (MYL-1501D Process VI minus MYL-1501D Process V) of mean change from baseline for HbA1c is no greater than 0.4% at 18 weeks of treatment.

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LIST OF COMMONLY USED ABBREVIATIONS

ADA	American Diabetes Association
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
cm	centimeter
CI	Confidence interval
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of Variation
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCVAb	Hepatitis C antibodies
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IRB	Institutional Review Board
S/IWRS	Interactive Voice Response System/ Interactive Web Response System
ITT	Intent to treat
IU	International Unit
kg	kilogram
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Milliliter
MMRM	Mixed Model Repeated Measures
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PSRM	Product Safety and Risk Management
REML	Restricted maximum likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SID	Subject Identification
SMBG	Self-monitored blood glucose
SOA	Schedule of Activities
SOP	Standard Operating Procedure
T1DM	Type 1 diabetes mellitus
TEAE	Treatment emergent adverse event
U	Unit
US	United States
WoCBP	Women of Child-Bearing Potential

1 STUDY DIAGRAM AND STUDY SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Conduct Section (Section 6) for detailed information on each procedure and assessment required for compliance with the protocol.

Figure 1: Study Diagram

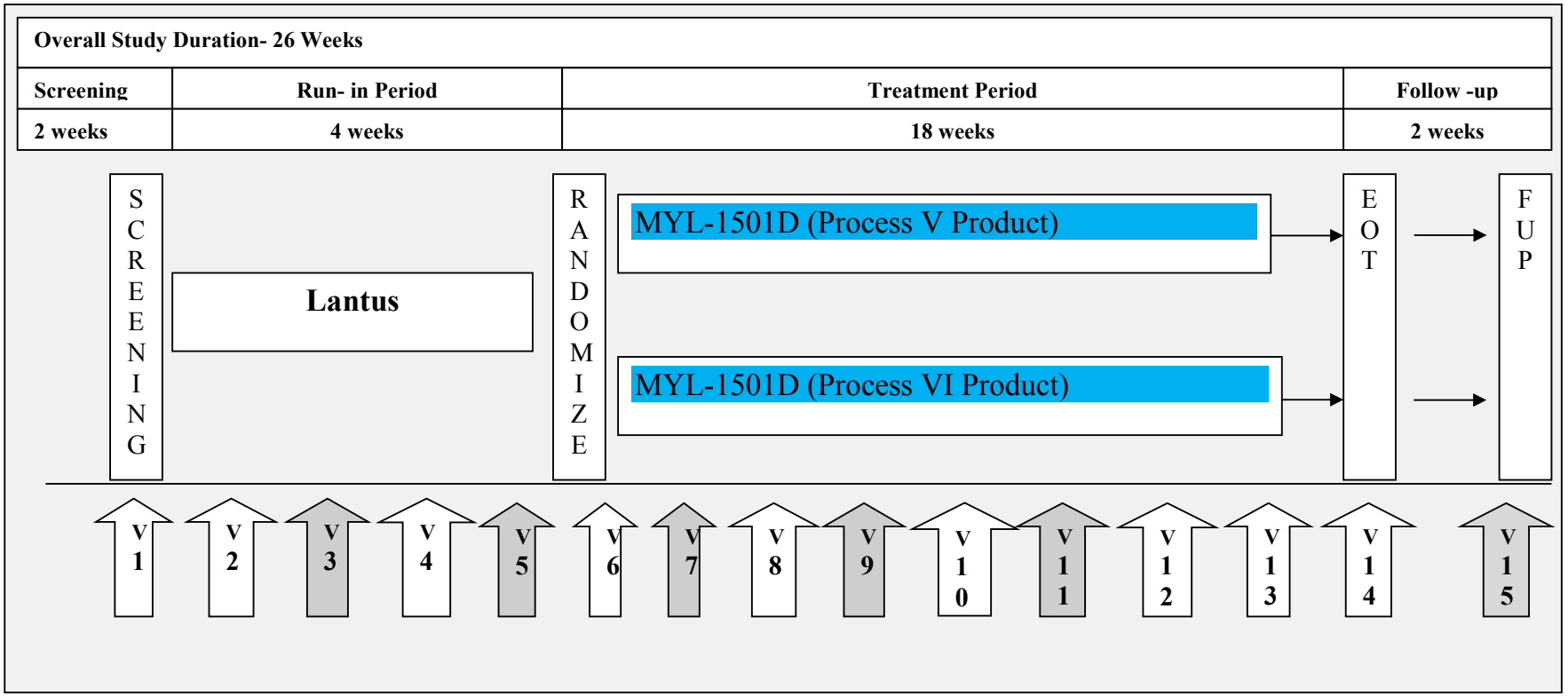

Table 1: Study Schedule of Activities

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									Follow-up
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	

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									Follow-up
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
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	
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	

Study Periods	Screening	Run-in Period				Randomized Comparative Treatment Period									Follow-up
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
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.

2 INTRODUCTION

2.1 Indication

MYL-1501D is being developed as a follow-on biologic (US terminology) or biosimilar (EU terminology) to Lantus®.

2.2 Background and Rationale

Insulin secretion in healthy subjects is characterized by relatively constant basal insulin secretion with a post-prandial surge. Type 1 diabetes mellitus (T1DM) is characterized by loss of the insulin-producing beta-cells of the islets of Langerhans in the pancreas, leading to a deficiency of insulin. The main cause of beta-cell loss is a T-cell mediated autoimmune attack [1]. The principal treatment of patients with T1DM is initiation of insulin and diet control and careful monitoring of blood glucose levels.

The Diabetes Control and Complications Trial [2] and other trials [3] provide conclusive evidence that maintaining tight glycemic control can prevent or delay microvascular and macrovascular complications in patients with T1DM. A number of different insulin regimens have been proposed for treatment of patients with T1DM. It is generally accepted that the so-called basal-bolus insulin regimen (1 or 2 daily injections of long/intermediate-acting insulin covering basal insulin requirements in combination with 3 daily injections of short-/rapid acting insulin to cover meal-related insulin requirements) generally yields the best glycemic control in diabetes. Clear targets for plasma glucose levels have been recommended for basal-bolus insulin regimens [4].

Different insulin preparations are available for management of basal insulin requirements, including intermediate-acting insulins (neutral protamine Hagedorn insulin) and long-acting insulin analogs such as insulin glargine and insulin detemir. Long-acting insulin analogs have proven efficacy and offer good glucose control over 24 hours for a single dose. Insulin glargine is a long-acting insulin analogue allowing once-daily administration to cover basal insulin requirements for over 24 hours. After injection of Insulin glargine into the subcutaneous tissue, the acidic solution is neutralized; leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration versus time profile with a prolonged duration of action.

MYL-1501D is a human insulin analogue of r-DNA origin produced in the host organism *Pichia pastoris*. *P pastoris* is a methylotropic yeast that has been successfully used in the production of proteins.

The aim of this study is to demonstrate similar efficacy and safety between MYL-1501D product produced from two manufacturing processes in combination with insulin lispro in patients with T1DM.

Since the two investigational products have an identical presentation of prefilled pen to be used by the subjects during the treatment period, the subject and the treating physician will remain blinded to treatment assignment. Furthermore, the evaluation of the study endpoints, such as analysis of immunogenicity and glycosylated hemoglobin (HbA1c), will be performed in a blinded manner by blinded personnel. The sponsor team as well as the CRO team will also be blinded to the subject assigned treatment.

To ensure that both treatment arms are comparable at baseline with respect to drug-induced immune responses and other parameters, only subjects who have been on a stable dose of Lantus® for at least 3 months prior to screening will be included.

During the 4-week run-in period with Lantus® and Humalog®, the dose of insulin will be titrated (if required) to ensure diabetes control. The run-in period ensures comparable drug exposure for all subjects, and increases the likelihood of comparable immune responses at the start of the treatment period. An 18-week treatment period is an adequate period to detect differences in HbA1c of the treatment arms [5].

Dosing with MYL-1501D during treatment period and Lantus® during run-in period will be guided by self-monitored blood glucose (SMBG)-based glucose level assessments and by the titration committee as detailed in the insulin monitoring (titration committee) plan.

Rescue criteria based on HbA1c are defined based on week 12 HbA1c measurement, so that a potential worsening of metabolic control in subjects during the study can be identified and therapy modified at the discretion of the investigator.

A follow-up visit, 2 weeks after the end of treatment, will ensure the safety of all subjects after they stop the study medication and return to receiving approved medications.

Complete information for the study medication can be found in MYL-1501D Investigator's Brochure (IB). [6]

2.2.1 Rationale for Dose Selection

Only subjects who have been on a stable dose of Lantus® for at least 3 months prior to screening will be included in the study, thus subjects would be on a stable dose at study entry. If required, subject dose should be adjusted during the 4-week run-in period to stabilize the subjects. During the treatment period, dose adjustment should be avoided but it is permitted to ensure subject's stable state and safety.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objectives

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 change in HbA1c from baseline to week 18 when administered in combination with mealtime insulin lispro.

3.1.2 Other objectives

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 SMBG profile from baseline

3.2 Endpoints

3.2.1 Primary Endpoints

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

3.2.2 Secondary Endpoints

3.2.2.1 Efficacy

- Change in fasting plasma glucose from baseline
- Change in basal insulin, meal-time, and total insulin dose per unit body weight (U/kg) from baseline
- Change in 8-point SMBG profile from baseline

3.2.2.1 Safety

- Incidence of positive antibody response and change in antibody percentage binding from baseline.
- Change in hypoglycemia rate (30 day adjusted) from baseline and incidence of hypoglycemic events
- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Incidence of local reactions, systemic reactions and other adverse events
- Incidence of device-related safety assessment

4 STUDY POPULATION

4.1 Study Population

A total of 202 subjects with T1DM are planned to be randomized in this study, to receive MYL-1501D from either Process VI or Process V with a randomization ratio of 1:1.

A detailed description related to sample size determination is provided in Section 7.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Written and signed informed consent needs to be provided by subjects or their legal representatives before starting any protocol-specific procedures.

2. Male and female subjects between the ages of 18 to 65 years, both ages inclusive.

3. Subjects with an established diagnosis of T1DM per American Diabetes Association (ADA) 2017 criteria who also fulfil the following criteria:

    a. Initiation of insulin treatment within 6 months of T1DM diagnosis

    b. Treatment with basal-bolus insulin therapy for at least 1 year before screening

    c. Fasting plasma C-peptide <0.3 nmol/L (0.9 ng/mL) at screening

    d. Subject has been on once daily Lantus® or once daily Levemir® or once daily Toujeo® at stable dose (±15% variation in dose) for at least 3 months at screening

4. Body mass index (BMI) of 18.5 to 35 kg/m^2 at screening (both values inclusive).

5. Stable weight, with no more than 5 kg gain or loss in the 3 months prior to screening, this information will be collected by subject interview during medical history.

6. HbA1c ≤9.5% at screening.

7. Hemoglobin ≥9.0 g/dL at screening.

8. Subject has the capability of communicating appropriately with the investigator.

9. Subject is able and willing to comply with the requirements of the study protocol including the 8-point SMBG, completion of subject diary records and following a recommended diet and exercise plan for the entire duration of the study.

10. Female subjects of childbearing potential who are willing to use oral contraception or acceptable methods of contraception, (e.g., intra-uterine device, spermicidal gel plus

condom, diaphragm plus condom, etc.), from the time of screening and for the duration of the study, through study completion.

a. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

b. Postmenopausal females must have had no regular menstrual bleeding for at least 1 year prior to screening.

c. Female subjects who report surgical sterilization must have had the procedure at least 6 months prior to screening.

d. All female subjects of childbearing potential must have negative pregnancy test results at screening and at clinic visits, as per the SCHEDULE OF ACTIVITIES (SOA).

e. If female subjects have male partners who have undergone vasectomy, the vasectomy must have occurred more than 6 months prior to screening

4.2.2 Exclusion Criteria

Subject candidates must not be enrolled in the study if they meet any of the following criteria:

1. History or presence of a medical condition or disease that in the investigator's opinion would place the subject at an unacceptable risk from study participation.

2. History of hypersensitivity to any of the active or inactive ingredients of the insulin/insulin analogue preparations used in the study, OR history of significant allergic drug reactions.

3. History of use of animal insulin within the last 3 years or use of approved biosimilar insulin glargine at any time prior to study entry, except for subject who previously participated in MYL-1501D studies and were compliant with the study protocols.

4. History of use of a regular immunomodulator therapy in the 1 year prior to screening.

5. History of autoimmune disorders other than T1DM or insufficiently treated autoimmune thyroid disorders, judged clinically relevant by the investigator (recorded while collecting subject history).

6. History of ≥1 episodes of diabetic ketoacidosis or emergency room visits for uncontrolled diabetes leading to hospitalization within the 6 months prior to screening.

7. History of clinically significant acute bacterial, viral or fungal systemic infections in the last 4 weeks prior to screening (recorded while collecting subject history).

8. Any clinically significant abnormality in electrocardiogram (ECG) or safety laboratory tests (LFT, RFT, hematology or any other laboratory deemed clinically relevant by the investigator) conducted at screening and considered by the investigator to make the subject ineligible for the study.

9. Serological evidence of human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (HCVAb) at screening.

10. History of drug or alcohol dependence or abuse during the 1 year prior to screening.

11. Receipt of another investigational drug in the 3 months prior to screening (or as per local regulations), or if the screening visit is within 5 half-lives of another investigational drug received (whichever is longer), or scheduled to receive another investigational drug during the current study period.

12. Subjects with the following secondary complications of diabetes:

    a. Active proliferative retinopathy as confirmed by a dilated ophthalmoscopy examination / retinal photography (performed by a person legally authorized to do so) within the 6 months prior to screening.

    b. Clinical nephrotic syndrome or diabetic nephropathy with a serum creatinine level >1.5 times of upper limit of reference range at screening

    c. History of severe form of neuropathy or cardiac autonomic neuropathy, recorded while collecting subject history. Subjects with mild or moderate forms of neuropathy will be allowed.

    d. Subjects with a history of limb amputation as a complication of diabetes (at any time), or any vascular procedure during the 1 year prior to screening.

    e. History of diabetic foot or diabetic ulcers in the 1 year prior to screening.

13. Any elective surgery requiring hospitalization planned during the study period.

14. Clinically significant major organ disorder at the time of screening including:

    a. Uncontrolled hypertension, defined as stage 2 hypertension by Joint National Committee VII (even if therapy is ongoing, blood pressure ≥160 mm Hg systolic or ≥100 mm Hg diastolic).

    b. Uncontrolled hyperlipidemia (even if therapy is ongoing, LDL >160 mg/dL or triglycerides >500 mg/dL).

    c. Uncontrolled hyperthyroidism or hypothyroidism (subjects can be included if these conditions are controlled with thyroid hormones or anti-thyroid drugs).

    d. Impaired hepatic function (alanine transaminase [ALT] or aspartate transaminase [AST] value >2 times the upper limit of the reference range and/or serum bilirubin 1.5 times the upper limit of the reference range at the screening visit). Subjects with evidence of Gilbert's disease may be included in the study if they have total bilirubin of <3 mg/dL with indirect bilirubin contributing to >80% of the total bilirubin.

15. History of a significant medical condition, such as:

a. Clinically significant cardiac disease like unstable angina, myocardial infarction, grade 3 or 4 congestive heart failure (CHF) according to New York Heart Association criteria, valvular heart disease, cardiac arrhythmia requiring treatment, and pulmonary hypertension; during the year prior to screening.

b. Stroke or transient ischemic attack (TIA) in the 6 months before screening.

16. Subjects with major depressive illness in the last 3 years (those who have well controlled depression for 3 months on a stable dose of antidepressants, with no major depressive episodes in the last 3 years, can be included, even if they are on medication), subjects with history of other severe psychiatric diseases (manic depressive psychosis [MDP], schizophrenia), which in the opinion of the investigator precludes the subject from participating in the study (recorded while collecting subject history).

17. History of hematological disorders that can affect the reliability of HbA1c estimation (hemoglobinopathies, hemolytic anemia, sickle cell anemia, etc.).

18. Subjects using the following in the 3 months prior to screening:

    a. Insulin pump therapy

    b. Any anti-diabetic drugs other than the study insulins allowed by the protocol.

19. Moderate insulin resistance, defined as requiring insulin of ≥1.5 Ukg/day.

20. Subjects who have received ≥14 consecutive days of glucocorticoid therapy by oral, intravenous, inhaled or other routes that produce systemic effects within the past 1 year, or who have received steroids by any route (except intra-nasal, intra-ocular, and topical) within the 4 weeks immediately preceding screening.

21. Subjects diagnosed as having cancer (subjects with history of basal cell carcinoma, carcinoma in situ or squamous cell cancer of skin, or in remission >5 years, will be allowed).

22. Subjects who have donated blood or plasma in the 1 month prior to screening

4.2.3 Criteria for study drug termination, withdrawal from the study and study termination

Subjects will be free to request termination of study drug or withdrawal from the study at any time for any reason.

If, for any reason, a subject discontinues the study prematurely, the subject may be followed up upon consent and as detailed in the following withdrawal criteria.

Following are the withdrawal criteria:

1. Withdrawal of consent.

2. For female subjects, diagnosis of pregnancy or stated intention to become pregnant. Effort should be made by the site to obtain consent from the pregnant women, so that they are followed until delivery or termination.

3. At the investigator's discretion (following discussion with the sponsor medical monitor), for safety issues such as severe hypoglycemia or hypoglycemic unawareness. The site should request the subject consent to follow-up as per the SCHEDULE OF ACTIVITIES until the Week 20 (Follow-up visit).

4. At the investigator's discretion (following discussion with the sponsor medical monitor), in certain situations such as significant illness, hospitalization for surgery, or an SAE which in the opinion of the investigator warrants treatment withdrawal. The site should request the subject consent to follow-up as per the SCHEDULE OF ACTIVITIES until the Week 20 (Follow-up visit).

4.3 Contraception

4.3.1 Females - Non-childbearing Potential

Female subjects of non-childbearing potential must meet at least one of the following criteria:

1. Postmenopausal females, defined as:

   - Females who are 45-65 years of age who have been amenorrheic for at least 1 year **and** who are known to have a serum FSH level >30 IU/L in the absence of hormone replacement therapy.

2. Females who have a documented hysterectomy and/or bilateral oophorectomy.

All other females will be considered to be of childbearing potential.

4.3.2 Females - Childbearing Potential

Female subjects of child-bearing potential must use an acceptable, highly effective method of contraception (i.e. a method with a failure rate <1% when used consistently and correctly) starting from screening through to at least 7 days after the final dose of study drug. For this study, such methods include at least one of the following:

- Abstinence (periodic abstinence is not acceptable).
- Tubal ligation.
- Intrauterine device (IUD) of intrauterine system (IUS).
- Condom with spermicidal foam/gel/film/cream/suppository.
- Male partner who has had a vasectomy for at least 6 months. Male partners with vasectomies of <6 months are NOT considered protected.
- Hormonal contraceptives (oral, injected, transdermal or implanted) with the exception of low dose gestagens, i.e. only containing lynestrenol or norethisterone, since they do not inhibit ovulation and are therefore not considered as highly-effective. The subject must remain on the hormonal contraceptive throughout the study and must have been using hormonal contraceptives for an adequate period prior to the study to ensure effectiveness (e.g., 3 months).

4.4 Pregnancy Testing

Serum or urinary pregnancy testing will be performed on all females of childbearing potential as described in the schedule of activities (results will be reviewed and must be negative prior to dosing). In the event of a positive test, the subject will be withdrawn from the study (or will not enter the study if during screening).

Any pregnancy occurring after randomization to study drug will be followed up and reported to the sponsor as per Section 9.4.1.

5 STUDY DRUG

5.1 Investigational Drug

During Treatment period, subjects will be randomized to receive one of the following;

MYL-1501D Product from Process V (100 U/mL)

or

MYL-1501D Product from Process VI (100 U/mL)

Additional treatment drugs provided during the study which are not investigational study drugs are detailed below:

During the run-in period, subject will receive Lantus® manufactured by Sanofi-Aventis for the US (US listed drug), 100 U/mL.

All subjects will receive Humalog® (insulin lispro injection, 100 U/mL), manufactured by Eli Lilly throughout the study.

MYL-1501D will be packaged and labelled according to all local legal requirements.

Clinical Supplies will provide prepackaged supplies for each subject. A kit will be assigned at randomization using the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS).

A label will be attached to the outside of each kit. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Subject number/study center number
- Contents and quantity
- Lot number
- Randomization code/kit number
- Investigator name
- Storage instructions
- Caution statement (for clinical study use only)
- Expiry date
- Mylan's name and address

5.1.1 Administration of Study Drugs

During the **Run-in period,** all subjects will receive Lantus® from Sanofi-Aventis (US listed drug) 100 U/mL until randomization. In addition, all subjects will be shifted from their current mealtime insulin to Humalog® at the start of the run-in period, and will continue on this for the complete study. The doses of Lantus® and Humalog® will be titrated (if required) during the run-in period to ensure diabetes control.

During **Treatment period,** all subjects will receive one of the following treatments;

MYL-1501D product from Process VI or Process V. Both investigational products will be provided in a pre-filled disposable pen with a 3-mL cartridge. During the treatment period, dose titration will be kept to a minimum.

In addition, all subjects will receive Humalog® (insulin lispro injection, 100 U/mL), manufactured by Eli Lilly.

In the event of any significant dosing errors, the CRO contact person and/or CRO medical monitor, or Mylan study contact should be informed immediately.

5.2 Study Medication/Device Complaints

In the event the subject has a complaint/concern during study participation regarding the medication/device supplied, they should contact the site.

In the event of a complaint/concern regarding any medication/device provided by Mylan for this study, at a minimum the following information should be sent by the site via e-mail to Clinicalbiologicscomplaints@mylan.com.

- Study number.
- Principal Investigator name.
- Subject ID.
- Date of occurrence of incident/complaint.
- Description of incident/complaint (facts).
- Confirmation if the complaint caused or resulted in a SAE? If “Yes”, confirmation that the SAE has been reported.

Additional information and potentially the return of study medication may be requested by Mylan such that the complaint can be investigated.

5.3 Storage, Disposition of Unused Study Drug and Drug Accountability

The Investigator, or an approved representative, e.g. pharmacist, will ensure that all investigational products are stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements while at the investigator site.

Study drug should be stored in accordance with the drug label. Storage conditions stated in the Investigator’s Brochure may be superseded by the label storage.

Temperature of storage facilities should be monitored and recorded on a daily basis using validated devices that record maximum and minimum temperatures. Should the storage facility experience any excursion of temperature outside of the labelled storage condition this must be reported immediately to Mylan or designee. At sites where daily monitoring and recording is not possible on weekends, the temperature record (e.g. max/min thermometers) should be checked immediately for any temperature excursions on the next working day after the weekend. Devices used for temperature monitoring should be regularly calibrated. Affected material must be placed into quarantine until the impact of the excursion has been assessed and confirmed by Mylan.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the study drug. Drug accountability forms must be used. Alternatively, Mylan

may approve use of standard institution forms. In either case, the forms must identify the study drug, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Mylan or designee.

At the end of the study, Mylan will provide instructions with regards to disposition of any unused investigational product. If Mylan authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Mylan. Destruction must be adequately documented.

5.4 Randomization

Assignment of Subject Identification number (SID), randomization number and study medication, as well as site drug inventory control will be managed by an automated IVRS/IWRS. A manual containing complete instructions for Web or telephone access and use will be provided to each site prior to study start. The IVRS/IWRS will assign a SID for each subject's first clinic visit. Each SID will be unique and serve as the primary subject identifier throughout all phases of the study. The SID must appear on all case report form (CRF) pages, source documents, laboratory data, ECG and diary data. Subjects qualifying to enter the study drug treatment phase, will be assigned an additional "randomization number" by the IVRS/IWRS at randomization. Dynamic allocation with minimization algorithm will be used for treatment randomization. Randomization will be stratified by investigator and basal insulin (Glargine) dose time (morning or evening).

5.5 Breaking the Blind

Regardless of the assigned treatment arm, all subjects in the study are provided with active anti-diabetic treatment, Insulin glargine.

The blinded treatment code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Qualified Investigator to complete a serious adverse event report or the clinical report. In such situations, the randomization information will be held by designated individual(s), and the date and reason for breaking the blind must be recorded. If possible, the CRO project manager should be contacted by telephone prior to unblinding but no later than 24 hours after unblinding. The investigator should follow the study's randomization procedures and should ensure that the code is broken only in accordance with the protocol. As the study is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s). Unblinding of treatment code for final data analysis will be done after database lock. Unblinding process will be performed in accordance to both sponsor's and CRO's unblinding SOPs, as detailed in the statistical analysis plan.

5.6 Concomitant Medications

All concomitant medications taken during the study (from signing informed consent to post-study follow-up) must be recorded with indication, daily dose, and start and stop dates of administration in the CRF. All subjects will be questioned about concomitant medication at each clinic visit and at follow up.

Medications taken within 28 days prior to screening and prior to dosing with study medication will be documented as a prior medication. Medications taken after dosing with study medication will be documented as concomitant medications.

Other than study drugs, insulin, insulin analogs and other anti-diabetes medications as well as glucocorticoid therapy (oral, intravenous, inhaled or other routes that produce systemic effects) are prohibited during the study (including the run-in period and the treatment period), except in case of rescue medication treatment.

A list of medications that may interfere with the effect of insulin is provided in Table 2. ***No drugs listed in this table should be started during the run-in period or treatment period.***

Table 2: Medication not to be started during the Run-in or Treatment period

Drug classes that are known to **augment** the blood glucose lowering effect of insulin such as:	Drugs and drug classes that are known to **decrease** the blood glucose lowering effect of insulin such as:
1. salicylates at doses more than >2 g/day 2. sulfa antibiotics 3. angiotensin converting enzyme inhibitors 4. disopyramide 5. fibrates 6. fluoxetine 7. monoamine oxidase inhibitors 8. propoxyphene 9. pentoxifylline 10. somatostatin analogs 11. bromergocryptine (bromocryptine) 12. anabolic steroids.	1. danazol 2. niacin 3. diuretics 4. sympathomimetic agents 5. glucagon 6. isoniazid 7. somatropin 8. thyroid hormones 9. oral contraceptives 10. estrogens 11. progestogens 12. protease inhibitors 13. phenothiazine derivatives 14. atypical antipsychotic medications (e.g. olanzapine and clozapine).

Subjects will abstain from all prohibited medications as described in the exclusion criteria section of this protocol (Section 4.2.2). Use of prohibited medication during the study will be deemed a protocol deviation and such subjects will be assessed by Mylan or designee regarding the potential need to early terminate study drug (e.g. for safety reasons: see Section 4.3.4).

5.7 Recommended Procedure for Subject Experiencing Adverse Effects Secondary to Excessive Pharmacological Effects of Study Drug

The following rescue criterion will be implemented to protect the safety of subjects during the study:

"Worsening of HbA1c by >1.0% compared to baseline at 12 weeks post randomization".

If the subject meets the criterion the investigator can switch the subject to Lantus® provided as part of the study at week 15 (Visit 13) or earlier, and continue with the study activities and procedures until the end of the study.

6 STUDY CONDUCT

Subjects eligible for study recruitment will have the nature, purpose, and risks of the study explained to them by the investigator. They will be provided with a written copy of the informed consent form (ICF) for the study and given sufficient time to consider the study's implications before deciding to participate. Subjects agreeing to participate in the study will sign the ICF and be given a duplicate copy before undergoing any screening or pre-screening (if required) procedures. A unique SID will be issued at the time of consent by IVRS/IWRS system.

Once a subject enrolls in this study, the site will make every effort to retain the subject for the planned duration of the study. Clinical study site staff are responsible for developing and implementing support and retention plans. Elements of this plan may include the following.

- Thorough explanation of the complete clinical study visit schedule and procedural requirements during the informed consent process and re-emphasis at each clinic visit.
- A simple explanation of the key data and key time points that are critical for the study's successful analysis, and the importance of all the treatment groups to the overall success of the study.
- Discussion at screening, and subsequent regular review of possible barriers to clinic visit attendance and full study participation and compliance.
- Collection of contact information at screening (address, phone numbers, email), which is regularly reviewed at subsequent clinic visits.
- Use of appropriate and timely study visit reminders.
- Immediate and multifaceted follow-up on missed clinic visits, including the possible use of trained staff to complete in-person contact with subjects at their homes.

In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study. All contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up." For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the CRF. Regardless of site plans to support and retain subjects within the study, subjects may voluntarily withdraw from the study for any reason and at any time.

For a subject that completes the study and all procedures it is anticipated that the duration of study would be up to 26 weeks.

For details and timings of assessments, refer to Section 6.5.

6.1 Screening Procedures

Each prospective subject must agree to participate in screening procedures by signing the most recent ICF before any screening procedure is initiated. The Principal Investigator or

Medical Sub-Investigator will review the inclusion and exclusion criteria to confirm eligibility of each subject prior to enrolment.

6.1.1 Screening (Visit 1 [Week -6 to Week -4])

Subjects will commence screening procedures within 6 weeks prior to randomization, to confirm that they meet the selection criteria for the study. If the time between screening procedures and potential randomization exceeds 6 weeks as a result of unexpected delays, then the subject will need to be discussed with Mylan or designee to consider potential for re-screening (if re screening is agreed, the subject will need to be re consented and assigned a new SID via IVRS/IWRS). Re-screening for other reasons may be possible following discussion with the Mylan or designee. If re screening occurs this will be clearly documented within the site file.

The following will be completed in during the visit:

- Obtain written informed consent before any study-related procedure is initiated, including the cessation of prohibited concomitant therapy. A copy of the signed ICF (including subject information sheet) will be given to the subject (and IHS-810 form for subjects recruited from US).
- Check selection criteria suitability
- Perform dilated ophthalmoscopy / retinal photography (if it was not done in the last 6 months) to exclude active proliferative retinopathy
- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record demographic details (age, height, gender, and race)
- Record body weight and calculate BMI
- Record medical history, concomitant illnesses and concomitant medications
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate)
- Record detailed history of all previous insulin use
- Perform and document physical examination
- Perform 12-lead ECG (supine, after 5 minutes rest) and document results
- Collect blood and urine samples for the following laboratory assessments:
    - Fasting C-peptide
    - Serum pregnancy test for women of childbearing potential
    - HIV, HBsAg, and HCVAb
    - Hematology
    - Blood chemistry
    - Urine analysis
    - HbA1c
    - Fasting plasma glucose
    - Fasting lipid profile
    - Immunogenicity analysis

For suspected lab errors, 1 repeat of the specific test will be allowed during the 14-day screening period.

After all assessments (except immunogenicity) have been performed, the investigator will assess the results for compliance with the inclusion and exclusion criteria. If all inclusion

criteria have been fulfilled and none of the exclusion criteria were met, the subject may be enrolled into the run-in phase. The run-in visit must be scheduled no later than 14 days after the start of the screening phase (date of subject signature on ICF).

6.2 Run-in Period

6.2.1 Visit 2 (Week -4)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Collect blood sample for fasting plasma glucose
- Dispense subject diary to the subject and provide information regarding the completion requirements and necessary glucose measurements provided.
- Review current dosing of Lantus and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Dispense study medication and provide dose and titration instructions
- Dispense ancillary supplies

6.2.2 Visit 3 (Week -3), Visit 5 (Week -1)

These visits can be performed as telephone contacts if preferred by site and subject. If the visit is performed as a telephone contact, a time and date must be agreed in advance by both parties and the subject must have the completed subject diary available for discussion of the entries during the call.

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of Lantus and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change

6.2.3 Visit 4 (Week -2)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood sample for fasting plasma glucose
- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of Lantus and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided.

6.3 Treatment phase

6.3.1 Visit 6 (Week 0)

After completion of the run-in phase without any major violation of the selection criteria the subjects will enter the randomized study treatment phase. During this visit the following procedures and assessments will be performed:

- Check selection criteria suitability
- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record body weight and calculate BMI
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate)
- Perform and document physical examination
- Perform 12-lead ECG (supine, after 5 minutes rest) and document results
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
    - Serum and urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
    - Fasting plasma glucose
    - HbA1c
    - Hematology
    - Blood chemistry
    - Urine analysis
    - Fasting lipid profile
    - Immunogenicity analysis (collect blood sample prior to study drug administration)
    - PK analysis (collect blood sample prior to study drug administration)

- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of Lantus and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Dispense study medication MYL-1501D (product from Process VI or Process V), and Humalog
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided.
- Perform randomization and document result

6.3.2 Visit 7 (Week 1), Visit 9 (Week 4), Visit 11 (Week 9)

These visits can be performed as telephone contacts if preferred by site and subject. If the visit is performed as a telephone contact, a time and date must be agreed in advance by both parties and the subject must have the completed subject diary available for discussion of the entries during the call.

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change

6.3.3 Visit 8 (Week 2), Visit 10 (Week 6)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
    - Urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
    - Fasting plasma glucose
    - Immunogenicity analysis (collect blood sample prior to study drug administration as outlined in Table 1)
    - PK analysis (collect blood sample prior to study drug administration as outlined in Table 1)

- Review the results of 8-point SMBG measurements, performed on 3 days during the week, only for visit 10.
- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided.
- Only applicable to Visit 10, Dispense study medication MYL-1501D (product from Process VI or Process V) and Humalog

6.3.4 Visit 12 (Week 12)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate)
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
    - Urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
    - Fasting plasma glucose
    - HbA1c
    - Fasting lipid profile
    - Immunogenicity analysis (collect blood sample prior to study drug administration as outlined in Table 1)
    - PK analysis (collect blood sample prior to study drug administration as outlined in Table 1)
- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Dispense study medication MYL-1501D (product from Process VI or Process V) and Humalog
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided

6.3.5 Visit 13 (Week 15)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record concomitant medications since previous visit
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
    - Serum and urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Perform drug accountability and check for treatment compliance

6.3.6 Visit 14/ End of Treatment (Week 18)

During this visit the following procedures and assessments will be performed:

- Discuss and check compliance to standard of care specifics as per ADA 2017 guidelines, self-management of diabetes and life-style modifications with the subject
- Record body weight and calculate BMI
- Record concomitant medications since previous visit
- Record vital signs (sitting after 5 minutes rest; pulse, blood pressure, temperature and respiratory rate)
- Perform 12-lead ECG (supine, after 5 minutes rest) and document results
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit
- Record device safety information
- Collect blood and urine samples for the following laboratory assessments:
    - Urine pregnancy test for women of childbearing potential (only a negative urine test result is needed for dispensing drug)
    - Fasting plasma glucose
    - HbA1c
    - Hematology
    - Blood chemistry
    - Urine analysis
    - Fasting lipid profile
    - Immunogenicity analysis (collect blood sample prior to study drug administration as outlined in Table 1)
    - PK analysis (collect blood sample prior to study drug administration as outlined in Table 1)
- Review the results of 8-point SMBG measurements, performed on 3 days during the week
- Review current dosing of MYL-1501D (product from Process VI or Process V) and Humalog and if necessary provide new dosing instructions and document the new dose and reason for change
- Perform drug accountability and check for treatment compliance
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided

6.3.7 Early study drug Termination (ET) visit

Subjects may request termination of study drug or withdrawal from the study at any time, or be required to withdraw or terminate study drug by the investigator or sponsor for reasons as per Section 4.3.4. If study drug is terminated or the subject withdraws or is withdrawn, the reason for termination/withdrawal should be established and recorded. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the outcome of subject contact attempt, if possible. The investigator will contact Mylan or designee, if subject fails to complete the study or violates the protocol.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Unless consent is withdrawn, subjects who prematurely terminate study drug will be asked to return to the clinic to conduct the ET visit as soon as possible after their last dose of study drug, and in case consent subject will be asked to conduct all the remaining visits according to study schedule table until the end of the study.

At the ET visit the End of Treatment visit (Week 18/Visit 14), procedures should be completed.

The site should explain the importance of data collection and make every effort to consent the subject to continue follow up per the SCHEDULE OF ACTIVITIES until Week 20 visit.

6.4 Visit 15 Follow up (Week 20) (telephone call)

- Record AEs, SAEs, local and systemic allergic reactions and severe hypoglycemic which are classified as SAE.
- Record concomitant medications since previous visit

6.5 Treatment Procedures

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator or designated representative will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator or designated representative will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The Mylan study team will be informed of these incidents in a timely fashion.

Activities specific to this protocol are expanded upon further below.

6.5.1 Blood Volume

Total blood sampling volume for an individual subject is approximately 235 mL.

Table 3: Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Safety Labs	30	1	3	120
PK[1]	4		5	20
Anti-drug antibody (ADA)[2]	10	1	5	60
Supplemental Immunogenicity[3]	10 (baseline), 5 (V1, V8, V10, V12, V14)	1	5	35
TOTAL				**235**

[1] Blood samples (1 x 4 mL) will be drawn into K_2EDTA plasma tubes.
[2] Blood samples (2 x 5 mL) will be drawn into serum separator tubes (SST).
[3] Blood samples (1 x 5 mL; 2 x 5 mL at baseline) will be drawn into serum separator tubes (SST).

6.5.2 Safety Testing Assessments

Safety will be assessed through physical examinations, monitoring of vital signs, 12-lead electrocardiograms, laboratory analyses, and adverse event monitoring.

6.5.2.1 Adverse Event Assessment

If a subject reports any symptoms after the signing of the informed consent form, they will be evaluated by medical staff and necessary measurements will be performed. The Principal Investigator or Medical Sub-Investigator will be notified before dosing to determine the course of action.

Clinically relevant findings from screening procedures, e.g., laboratory tests or physical examinations will be recorded as medical history. Clinically significant changes from the screening procedures results will be recorded as adverse events.

Subjects will be routinely queried with regard to the presence or absence of adverse events using open ended questions. The clinic will provide documentation of any adverse events in the subject's CRF. The adverse event source documentation will minimally include the following information: date and time of assessment, the outcome of the response, and identification of the clinic staff member collecting the information.

6.5.2.2 Hypoglycemia

Incidence of hypoglycemic episodes will also be summarized by category (Severe Hypoglycemia, Documented Symptomatic Hypoglycemia, Asymptomatic Hypoglycemia, Probable Symptomatic Hypoglycemia, Relative Hypoglycemia and Nocturnal Hypoglycemia). In addition, nocturnal hypoglycemia rate and incidence will be analyzed in a same way as overall hypoglycemic episodes.

Hypoglycemia is a state produced by a lower than normal level of glucose in the blood. This may develop, if for example:

- The subject misses or delays meals or there is a change in diet
- The subject takes a higher dose of study drug than prescribed
- The subject consumes alcohol
- The subject does more intense or longer physical exercise or work than normal,

- The subject is recovering from an injury, operation, fever or other illness, or from other forms of stress

6.5.2.2.1 Classification

A. Severe Hypoglycemia

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

B. Documented Symptomatic Hypoglycemia

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

C. Asymptomatic Hypoglycemia

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

D. Probable Symptomatic Hypoglycemia.

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

E. Relative Hypoglycemia.

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

F. Nocturnal Hypoglycemia.

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

Note: A diagnosis of severe hypoglycemia as per above classification will always be considered as serious adverse event. Other hypoglycemic episodes which fulfils ICH criteria for seriousness (life-threatening, hospitalization etc.) or represent important medical events based on investigator's judgment should also be reported to sponsor within 24 hours.

6.5.2.2.2 Identification of Hypoglycemia

Symptoms of hypoglycemia include but are not limited to the following: palpitations, sweating, hunger, nervousness and shakiness, perspiration, dizziness or light–headedness,

sleepiness, confusion, difficulty speaking, feeling anxious or weak. Neuroglycopenic manifestations may include seizure, coma, and even death.

Subject will be instructed to be alert for signs and symptoms of hypoglycemia; and if possible to take glucose meter readings at the time of the episode and to record the details of the episode with any remedial action taken and the blood glucose level (if it was checked) in their diary.

Investigators will instruct the subjects on self-management of hypoglycemic episodes. Investigators will also instruct subjects on remedial actions to be taken during the episodes of severe hypoglycemia. Subject will be encouraged to call the study site if they experience hypoglycemia.

6.5.2.2.3 Management of Hypoglycemia

The following steps are recommended for managing hypoglycemic episodes:

1. The subject should begin with 15 to 20 grams carbohydrate (e.g., 3-4 teaspoons of table sugar dissolved in water, 1 tablespoon of honey, ¾ cup of juice or regular soft drink, 3-4 glucose tablets).

2. Subsequently, if the glucose level is ≤50 mg/dL, then the subject will be asked to consume 20 to 30 grams carbohydrate (e.g., 4-6 teaspoons of table sugar dissolved in water, 2 tablespoons of honey, ¾ cup of juice or regular soft drink, 4-5 glucose tablets).

3. Subject will be asked to recheck blood glucose after 15 minutes and to repeat hypoglycemia treatment if the blood glucose does not return to normal after 15 minutes. If the next meal is more than 1 hour away, subjects should follow with additional carbohydrate or a snack.

4. If hypoglycemia persists after the second treatment, subject or companion should be instructed to contact the investigator.

It is recommended that the subjects always carry some sugar lumps, sweets, biscuits, or sugary fruit juice.

For an event of severe hypoglycemia, the subject can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate training, or glucose given intravenously by a medical professional. Intravenous glucose can also be given if the subject does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness administration of oral carbohydrate is recommended in order to prevent a relapse.

Full hypoglycemic episode documentation includes time of occurrence, duration, time of recovery, remedial measures undertaken, recording the symptoms and plasma glucose / SMBG levels at the beginning and end of the episode with time and date, and classification in to the different subtypes (Refer to Section 6.5.2.2.1).

6.5.2.2.4 Reporting of hypoglycemic episodes

Hypoglycemic events and any associated symptoms are recorded only on the hypoglycemic episodes page of the CRF. Severe hypoglycemia and those episodes meeting any of the ICH

seriousness criteria (Section 9.2.4) are also to be notified as SAEs to the Mylan Global Product Safety and Risk Management department, as described in Section 9.3.2.8; and entered on the SAE and AE pages.

6.5.2.3 Laboratory Safety

The following safety laboratory tests will be performed at times defined in the study schedules in Sections 1 and Section 6.

Table 4: Laboratory Safety Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea and Creatinine Glucose Calcium Sodium Potassium Chloride AST, ALT Total Bilirubin Direct/Indirect bilirubin Alkaline phosphatase Uric acid Albumin Total protein CRP C-Peptide Lipid Profile	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy/culture[a]	Urine hCG HIV and HBsAg and HCVAb HbA1c
[a] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.			

Hematology and chemistry will be analyzed by central laboratory. Urinalysis will be conducted by dipstick at site and if urine is positive for blood, protein, nitrites, or leukocyte esterase, will be analyzed via microscopy/culture by a central laboratory.

Blood volumes to be collected and blood and urine sample handling instructions will be provided in the central vendor laboratory manual. The central laboratory will provide collection materials and directions for packaging and shipment of samples.

Any clinically significant findings in laboratory safety data should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.5.2.4 Immunogenicity Assessment

Blood samples of 5 mL each will be taken into serum separator tubes at each time point as outlined in Table 1. At Visits 1, 8, 10, 12, and 14, three blood samples will be drawn, whereas at Visit 6 (baseline) four blood samples will be drawn. The blood samples will be taken by direct venipuncture, and the exact times of blood sampling will be recorded in the CRF. Two of the samples will be used to determine the presence of anti-drug antibodies against insulin glargine using the approach outlined below. The other sample will be collected and stored in reserve for potential supplemental immunogenicity testing and/or characterization. Samples collected pre-dose at the randomization visit (Visit 6) will be considered as baseline. Samples collected at screening and the supplemental samples

collected at baseline may also be used for method development and validation. Sample handling instructions are specified in the laboratory manual.

A conventional radioimmunoprecipitation assay will be employed for the assessment of anti-drug antibodies in clinical samples. In this assay, samples will undergo a pre-treatment step that includes acid dissociation to release any anti-insulin antibodies complexed with free drug, followed by charcoal adsorption of the free insulin analog. The treated samples will be incubated with a fixed amount of ^{125}I-MYL-1501D, and anti-drug antibody complex formation with the tracer is measured via gamma counter and expressed as a percentage of bound to total radioactivity (%B/T).

The multi-tiered sample analysis recommendations for immunogenicity testing from published white papers [7, 8], and current regulatory guidance [9, 10], will be employed for the immunogenicity assessment of MYL-1501D Process V and Process VI. The antidrug antibody analysis methodology will be fully validated, and the sample analysis procedures will be documented in a Sample Analysis Protocol. Sample handling, processing, and storage instructions will be detailed in a separate manual. The laboratory for immunogenicity analysis will be designated by the Sponsor.

6.5.2.4.1 PK Assessment

One blood sample of 4 mL will be taken into a K_2EDTA plasma tube at each time point, as outlined in Table 1. The blood samples will be taken by direct venipuncture, and the exact times of blood sampling will be recorded in the CRF. The PK sample will be taken along with the immunogenicity samples. The exact time of last MYL-1501D dose prior to withdrawal of blood for PK will be noted. The blood samples will be analyzed for Insulin Glargine, Glargine M1 and M2 metabolite concentrations by Covance Laboratories Ltd. (Harrogate, UK) using a fully validated analytical method. Sample handling instructions are specified in the laboratory manual.

The PK samples are taken as outlined in Table 1. The PK sample will be taken during the visit, preferably taken 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.

6.5.2.5 Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Sections 1 and Section 6. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Blood pressure will be measured at sitting position, after 5 minutes rest.

The same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring blood pressure and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. Any clinically significant changes in blood pressure and pulse rate should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.5.2.6 12-lead ECG

In this study, 12-lead ECGs will be recorded using local ECG devices and review. ECGs should be collected at times specified in the study schedules in Sections 1 and Section 6.

All scheduled ECGs should be performed after the subject has rested quietly for at least 5 minutes in a supine position.

To ensure safety of the subjects, a medically qualified individual at the site will assess ECG recordings and make any comparisons to baseline measurements.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. Any clinically significant ECG abnormalities measured at screening should be assessed for their effects on subject eligibility of the study and recorded in medical history. ECG parameters will not be recorded in the CRFs, but any clinical significant changes between the screening and subsequent ECGs should be recorded as an AE. Determination of clinical significance and seriousness will be based on the Investigator's medical judgment.

6.5.2.7 General Physical Examination

A full general physical examination will consist of an examination of the abdomen, cardiovascular system, lungs, lymph nodes, musculoskeletal and neurological systems, skin, extremities, head, ears, eyes, nose, and thyroid gland by trained medical personnel at the site. A full physical examination will be performed at Visit 1 (screening), Visit 6 (randomization) and Visit 14 (EOT or ET).

Height and weight will be assessed at Visit 1. Physical examination results will not be recorded in the CRFs, but any clinical significant finding at Screening (Visit 1) should be recorded under medical history and changes between Screening (Visit 1) and subsequent examinations should be recorded as an AE. Determination of clinical significance and seriousness will be based on the investigator's medical judgment.

7 STATISTICAL ANALYSIS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

7.1 Sample Size Determination

A total of 202 subjects with T1DM are planned to be randomized for this study and will receive either MYL-1501D Process V product or MYL-1501D Process VI product, in a 1:1 ratio.

The sample size estimation is based on assumptions for the change from baseline up to week 18 in HbA1C with either MYL-1501D product from Process V or Process VI. It is assumed, that true mean groups mean difference is 0.03 and standard deviation is equal to 0.74. To demonstrate non-inferiority margin of 0.4% using a 2-sided 95% confidence interval and a 90% power, a total of 172 subjects (86 subjects per treatment group) are required.

To account for a maximum of 15% of subjects being not eligible for the per protocol analysis, a total sample size of 202 is planned to be randomized for this study. The true treatment difference and standard deviation is based on previous study MYL-GAIA-3001.

No replacement of subject will be performed if subject discontinued prematurely from the study.

7.2 Primary Endpoints

7.2.1 Definition of Primary Endpoints

The change in HbA1c from baseline up to week 18 is the primary endpoint for this study.

7.2.2 Statistical Methodology for Primary Endpoints

For the analysis of the primary endpoint all randomized subjects will be taken account – irrespective of whether subjects having post-baseline measurement. All scheduled non-missing data combined together with imputed missing data will be performed for primary analysis. Multiple imputed datasets will be generated based on the assumption of a monotone missing data pattern. The imputation will be performed using the monotone regression method for week 12 and week 18 sequentially. The variables treatment, pooled investigator, and basal insulin dose time will be used as independent variables.

Then the treatment effect will be estimated using a repeated measures analysis employing a restricted maximum likelihood (REML)-based, mixed model repeated measures (MMRM)-effects model approach. In this model all subjects will be used for the estimation of the 95% confidence interval of the difference between MYL-1501D Process VI product and Process V product for mean change in HbA1c at week 18. The MMRM model will include the fixed, categorical effect of treatment group assignment, visit, treatment group-by-visit interaction and the other fixed effect terms investigator, basal insulin dose time, and baseline HbA1c value as covariates.

Further details on the MMRM model will be provided in the SAP. Investigator pooling will be finalized before unblinding treatment to avoid introducing bias. The detailed method of investigator pooling will be documented in the SAP.

7.2.3 Primary Analysis for Primary Endpoints

For primary endpoint analysis, non-inferiority for efficacy will be established if the upper limit of a two sided 95% confidence interval for the absolute difference (MYL-1501D Process VI minus Process V) of mean change from baseline to endpoint for HbA1c is no greater than 0.4% at Week 18. The primary analysis will be performed on the intent to treat (ITT) analysis set.

7.2.4 Secondary/Sensitivity Analyses for Primary Endpoints

A further robustness check will be conducted using the PP population and applying the same MMRM procedure as described in previous section to establish non-inferiority. Any differences in the conclusion will be further investigated by examining differences between the ITT and the PP populations.

Other sensitivity analysis addressing missing data will be conducted in the following manner:

Same analysis approach as primary analysis without imputing missing values.

In another method, the imputed values will be corrected such that the full non-inferiority margin will be added for imputed values in Process VI group. All imputed datasets will be analyzed using the same model parameters as used in the primary analysis, and the results will be combined using Rubin's rules.

A standard last observation carried forward (LOCF) approach will be conducted such that missing data will be imputed by LOCF. This dataset will be analyzed for the ITT and PP populations using the ANCOVA model for which details will be described in the SAP.

7.2.5 Missing Data

The only imputed data will be performed in the primary and sensitivity analyses as described above for HbA1c. Otherwise, missing data will not be imputed.

7.2.6 Sub-Group Analyses

Subgroup analyses of important factors, including but not limited to factors such as age group, gender and race are planned for the key outcomes of HbA1c and immunogenicity variables. These will be conducted by adding factor and treatment-by-factor interactions to the MMRM model models of the main analyses. Other exploratory subgroup analyses may be performed, as deemed appropriate.

7.3 Secondary Endpoints

The following efficacy measures (both actual and change values) will be summarized at baseline and scheduled visit. Similar statistical analysis approach for primary will be performed for continuous variables without imputing missing values. Contrasts of LS mean at each scheduled visit will be used to evaluate all pairwise treatment comparisons, and 95% confidence intervals for treatment differences in LS means will be computed for each visit.

- Change in fasting plasma glucose from baseline
- Change in basal insulin, meal-time, and total insulin dose per unit body weight (U/kg) from baseline
- Change in 8-point SMBG profile from baseline.

All above analyses will be performed on ITT set.

The following safety measures (both actual and change values) will be summarized at baseline and scheduled visit. Contrasts of LS mean at each scheduled visit will be used to evaluate all pairwise treatment comparisons, and 95% confidence intervals for treatment differences in LS means will be computed for each visit. For categorical data analyses, Fisher's exact test or Chi-squared test will be used. The details will be provided in the SAP.

- Incidence of positive antibody response and change in antibody percentage binding from baseline.
- Change in hypoglycemia rate (30 day adjusted) from baseline and incidence of hypoglycemic events
- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Incidence of local allergic reactions, systemic allergic reactions and other adverse events
- Incidence of device-related safety assessment

The incidence of subjects with each of the three following criteria will be summarized descriptively (for categorical measures) by treatment to explore possible insulin neutralization effect:

- An increase of over 10% in cross reacting antibodies from baseline
- Increases in HbA1c of over 0.2% from baseline at any visit
- Increase in total or basal insulin dose at any visit

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

All above analyses will be performed on safety set.

7.4 Analysis Set Definitions

The ITT analysis set includes all randomized subjects (including subjects who receive incorrect treatment, do not complete the study or do not comply with the protocol or used prohibited medication).

The PP analysis set includes subjects who complete Week 18, and have HbA1c measurements as per the protocol, or have at least one post-baseline HbA1c data (for subjects who discontinue prematurely); and do not have protocol violations that impact the primary

outcome (as detailed in the statistical analysis plan). Subjects who meet rescue medication criteria and take rescue medication will be excluded from PP analysis set. The subjects excluded from the PP population will be identified before database lock (i.e., before unblinding the study team).

The safety analysis set includes subjects who take at least one dose of the study medication after randomization. For safety analyses, subjects will be categorized according to the treatment that they actually received.

7.5 Other Safety Analyses

The analysis set for safety summaries is defined as all subjects who received at least one dose of study medication in the randomized treatment period. Safety data from the run-in period will be presented in listings only.

Treatment emergent adverse events and concomitant medications will be summarized and listed. All AEs that occur after the first dose of double-blind study medication through 14 days after the last dose will be considered treatment emergent AEs. The number and percentage of subjects with at least one treatment emergent AE will be presented by treatment group and events further summarized by maximum severity and relationship to study medication.

Descriptive statistics will be provided for the following safety data. No inferential analysis of this safety data is planned. Any ECG, blood pressure, and pulse rate abnormalities of potential clinical concern will be described.

7.5.1 Vital Signs

Change from baseline of vital sign measurements will be analyzed using MMRM with model terms of pooled investigator, basal insulin dose time, treatment, visit, treatment-by-interaction as fixed effects, and baseline value as covariate. The descriptive statistics including actual measurement and change from baseline along with treatment comparison will be performed at scheduled visits.

The percentage of subjects in categories such as potentially clinically significant will be summarized and treatment comparison will be performed using Fisher’s exact test.

7.5.2 ECG Analyses

The percentage of subjects in categories such as abnormal/non-clinically significant and abnormal/clinically significant will be summarized and treatment comparison will be performed using Fisher’s exact test.

7.5.3 Laboratory Data

Change from baseline of laboratory measurements will be analyzed using MMRM with model terms of pooled investigator, basal insulin dose time, treatment, visit, treatment-by-visit interaction as fixed effects, and baseline value as covariate. The descriptive statistics for actual measurement and change from baseline along with treatment comparison will be performed at scheduled visits.

The percentage of subjects in categories such as abnormal/non-clinically significant and abnormal/clinically significant will be analyzed using Fisher's exact test. P-value for the two-sided test will be presented.

8 ADMINISTRATIVE PROCEDURES

8.1 Source Documentation Forms

All clinical data will be recorded by the clinical staff on raw data sheets and/or recorded electronically using validated software. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidance.

The nature and location of all source documents will be documented separately. Source data may be directly captured from devices, transferred from 3rd parties (e.g. laboratory data) or entered manually into CRF/database.

8.2 Access to Data/Source Documentation

The Investigator or designated representative will permit full access to data and source documentation for the purpose of clinical monitoring, audits, IRB/IEC review and regulatory inspections.

8.3 Final Clinical Study Report and Case Report Forms (CRFs)

A written clinical study report will be provided in accordance with the International Conference on Harmonization (ICH) E-3 guidelines including Annex I (Synopsis) documenting the clinical execution of the study. This report will include a description of any protocol deviations. The final report will also include reasons for withdrawals and any necessary treatment(s). The report will also include tables presenting demographics (separate summary tables for enrolled and completed subjects), and adverse events recorded during the study. In addition, the clinical study report will include a Quality Assurance statement, documenting that the report has been reviewed for completeness, accuracy, and compliance with the protocol and applicable local and federal regulations. For final clinical reporting purposes only, adverse events deemed “definite”, “probable” or “possible” will be included in the treatment-related summaries/listings.

Case Report Forms containing data transcribed from subject source documents (as appropriate) and copies of other source documents will be supplied by the clinical site. The Principal Investigator must sign each subject’s CRF after completion of data entry, signifying that the data entered in the CRF is complete and accurate. Electronic CRFs may be provided.

8.4 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well-being of the study subjects requires medical treatment, the study will be conducted as described in the approved protocol (and amendments, if applicable), GCP and applicable SOPs. In addition, the study will be conducted in accordance with the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted. Any deviation(s) from the protocol will be recorded and presented in the final report.

8.5 Data Handling and Record Retention

All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the study subjects remains protected.

A CRF is required to be completed for each subject receiving study medication. The CRF is property of the sponsor and the Investigator must review all CRFs prior to submission to the sponsor.

The CRF may be consider as the source document, the investigator must seek prospective agreement to the sponsor in writing to use the CRF as source document prior the start of the study. In addition, items directly recorded in the CRF must be documented that they will be considered as source.

All records pertaining to the receipt and return of study supplies (particularly study medication) and copies of final case report forms, worksheets, and other pertinent source documents must be retained in accordance with ICH-GCP and the applicable regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

The investigator must obtain in writing the sponsor's agreement to dispose of any records, even if the retention period has been reached.

8.6 Confidentiality

Information furnished to Clinical Investigators and IRBs/Ethics Committees will be maintained in confidence by the Clinical Investigator and IRB/Ethics Committee. By signing this protocol, the Investigator affirms to the Sponsor that he/she will maintain, in confidence, information furnished to the IRB/Ethics Committee relevant to this study under appropriate understanding of confidentiality with such IRB/Ethics Committee.

By signing the protocol, the Investigator agrees that within local regulatory restrictions and institutional and ethical considerations, the Sponsor may consult and/or copy source documents (e.g., laboratory/X-ray reports, ECG tracings, workbooks, medical records) in order to verify CRF data.

8.7 Ethics and Regulatory Authorities

Guidelines will be followed with regard to the treatment of human subjects in the study, in accordance with the requirements of the Declaration of Helsinki and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E6) in addition to the regulatory requirements of the country where the study is being conducted as well as the country where the study will be submitted.

8.7.1 Institutional Review Board/Ethics Committee

The Investigator is responsible for obtaining initial and continuing review (at intervals not more than once per year) of the study by an IRB/Ethics Committee, or in accordance with applicable government regulations of the country where the study is being conducted as well as the country where the study will be submitted. This study will not enroll any subjects until the IRB/Ethics Committee provides written approval of the protocol and the informed

consent to the investigator. In addition, a copy of the IRB/Ethics Committee approval documents must be provided to the sponsor prior to enrolling any subjects into the study.

8.7.2 Regulatory Authority

This clinical study protocol, title and a list of investigational sites, IEC(s)/IRB(s) approvals, as well as other relevant documentation will be submitted to the local Regulatory Authorities for review and approval prior to study start. Upon completion, the Regulatory Authorities will be notified the study has ended. The study will only be undertaken in compliance with the local regulatory requirements.

8.8 Informed Consent

A properly executed, written informed consent in compliance with current GCP guidelines and ICH guidelines shall be obtained from each volunteer prior to entering the study. A copy of the informed consent document to be used will be submitted by the investigator to an independent institutional review board (e.g. IRB or ethics committee) and the Sponsor and/or its agent for review and approval prior to the start of the study. The investigator shall provide a copy of the signed and dated informed consent to the subject, and a signed and dated copy shall be maintained in the volunteer's medical record.

8.9 Disclosure and Publication of Clinical Study Data

The disclosure and publication of clinical study data will be detailed in the clinical study agreement with the Investigators.

8.10 End of Study

The end of study is considered to be the date of last subject last visit or the date of early termination of the study whichever is the later.

9 ADVERSE EVENT REPORTING

9.1 Adverse events

All observed or subject-reported AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as outlined in this section.

The Investigator must pursue and obtain information adequate both to determine the outcome of all AEs and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Mylan. The Investigator is required to assess causality and should obtain sufficient information to determine the causality of all AEs. All AEs will be followed until the event is resolved, deemed to be stable, or until the event is found to be due to another known cause (concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted with the sponsor concurring with that assessment.

9.2 Definitions

9.2.1 Adverse Events

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 will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition.

An AE will be defined as a TEAE if the first onset (or worsening, in the case of pre-existing disease) is after the first administration of MYL-1501D after randomization through follow-up visit or 14 days after last dose [for subjects that do not have a follow-up visit].

9.2.2 Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose 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 study drug reported as “possible”, “probable” or “definite” will be considered ADRs. If the relationship to the study drug is not given, then the AE must be treated as if the relationship were “possible.”

9.2.3 Unexpected Adverse Event/Adverse Drug Reaction

An unexpected AE or ADR is defined as one whose nature or severity is not consistent with the applicable reference safety information designated for the study. For example, hepatic

necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

The reference safety document for MYL-1501D is the IB. For Humalog® and any concomitant medication, the respective SmPC or US prescribing information will be the reference safety document.

9.2.4 Serious Adverse Events

A SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
    - NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly.
    - NOTE: A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is considered an SAE. However, a newly diagnosed pregnancy in a patient that has received the study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy. The patient with newly diagnosed pregnancy will discontinue receiving study treatment and will be followed-up every 3 months until delivery or termination to gather information about the outcome of the pregnancy.
- Is an important medical event.
    - NOTE: Important Medical Event: Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient and / or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
    - For this protocol, any cancer, including localized basal cell carcinoma, is considered an important medical event, to be reported as a SAE.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
    - NOTE: Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. Events NOT to be reported as SAEs are hospitalizations for the following:
        - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
        - Treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.
        - Admission to a hospital or other institution for general care due to social or economic reasons (e.g., no access to local ambulatory medical care).

- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Hospitalization also does not include the following:

- Rehabilitation facilities.
- Hospice facilities.
- Respite care (e.g., caregiver relief).
- Skilled nursing facilities.
- Nursing homes.

Any non-serious AE that is determined by the medical monitor/sponsor to be serious (per company policy or regulatory requirements) will be communicated to the Investigator for reclassification. To assist in the determination of case seriousness further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical study.

9.3 Management of Adverse Events

AEs or SAEs will be collected from the time the subject signs the informed consent form until the follow-up visit or 14 days after last dose of study medication. Pre-existing diseases or conditions (reported at visit 1 in medical history) will not be considered as AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition. An SAE deemed to be related to the study drug by the Investigator in consultation with sponsor will be reported even after the Follow-up visit if reported by subjects.

9.3.1 Collection

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as described previously. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation. The Investigator will then monitor and/or ask about or evaluate AEs using non-leading questions, such as

- “How are you feeling?”
- “Have you experienced any issues since your last visit?”
- “Have you taken any new medications since your last visit?”

Any clinically relevant observations made by the Investigator during the visit will also be considered AEs.

The Subject’s diary should also be reviewed at each study visit for adverse events. At week 0 visit when study diaries are issued, subjects will be appropriately educated by the study designee on what constitutes an adverse event and instructed to record adverse events in the study diary in a timely manner.

9.3.2 Evaluation

9.3.2.1 Severity Assessment of Adverse Events

The clinical severity of an AE will be graded using the NCI-CTCAE Criteria Version 4.03. A copy of these criteria will be provided to each study site. If an AE is not listed in the CTCAE, its clinical severity will be classified as follows:

Table 5: Clinical Severity of Adverse Events

The Investigator will use the terms defined below to describe the maximum intensity of the AE.	
Grade 1 – MILD	Does not interfere with subject's usual function.
Grade 2 – MODERATE	Interferes to some extent with subject's usual function.
Grade 3 – SEVERE	Interferes significantly with subject's usual function.
Grade 4 - LIFE-THREATENING	Risk of death at time of event
Grade 5 – DEATH	Death related to AE

If an AE is graded 4 or 5 according to the above criteria, then the AE meets the criteria for an SAE and the Investigator should immediately notify the sponsor or designee as described in Section 9.3.2.8.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity based on the CTCAE grading or on the above table, whereas an SAE is an AE that meets any of the regulatory specified criteria required for designation as seriousness described in Section 9.2.4.

9.3.2.2 Action Taken

The possible actions taken for an AE are described in Table 6.

Table 6: Action Taken for an Adverse Event

Dose reduced	The dose regimen was reduced by changing its frequency, strength, or amount.
Dose increased	The dose regimen was increased by changing its frequency, strength, or amount.
Treatment interrupted	The treatment was temporarily interrupted.
Treatment withdrawn	The treatment was permanently discontinued.
Concomitant therapy or procedures	Treatment was needed as a result of the AE (the concomitant treatment should be recorded on the relevant page of the CRF).
Unknown	Not known, not observed, not recorded, or refused.
No action taken	The AE did not require any intervention.
Not applicable	AE occurred after study medication was permanently withdrawn or subject completed the treatment period.

9.3.2.3 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

All ongoing AEs without fatal outcome (i.e. did not cause death) will be recorded as not recovered/not resolved at the time of death.

*Only select fatal as an outcome when the AE results in death. If more than one AE is possibly related to the subject's death, the outcome of death should be indicated for the AE which is the most plausible cause of death in the opinion of the Investigator.

Note: although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

9.3.2.4 Causality Assessment of Adverse Events

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. The Investigator must make an assessment of the relationship of each AE (serious and non-serious) to the study treatment(s) and record this relationship in the CRF.

In addition, if the Investigator determines an AE or SAE is associated with study procedures, the Investigator must record this information about the causal relationship in the source documents and CRF, as appropriate, and report the assessment in accordance with the reporting requirements, as applicable, AE or SAE.

Factors that need to be considered when making a causality assessment include:

- Temporal relationship (e.g., time of onset)
- Clinical and pathological characteristics of the event(s)
- Pharmacological plausibility
- Exclusion of confounding factors (medical and medication history)
- Drug Interactions
- De-challenge/re-challenge
- Dose relationship

A suspected relationship (definite, probable, and possible) between the events and the study medication means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. Receipt of additional or clarifying information may warrant reassessment of causality. The Investigator is responsible for assessing relationship of AEs to study treatment in accordance with the following definitions:

Table 7: Definition of Suspected Relationship between the Events and Study Medication

DEFINITELY	Causal relationship is certain	For Example: the temporal relationship between drug exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLY	High degree of certainty for causal relationship	For Example: the temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other

		causes have been eliminated or are unlikely.
POSSIBLY	Causal relationship is uncertain	For Example: the temporal relationship between drug exposure and the AE onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal, and while other potential causes may or may not exist, a causal relationship to study drug does not appear probable
UNLIKELY	Not reasonably related although a causal relationship cannot be ruled out	For Example: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible), or disease or other drugs provide plausible explanations
UNRELATED/NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible

For SAEs, the relationship to the study treatment(s) is considered to be unlikely or not related/unrelated, an alternative suspected etiology should preferably be provided (e.g., concomitant medications, intercurrent condition) wherever applicable and available.

9.3.2.5 Documentation

All AEs occurring within the period of observation for the study must be documented in the CRF with the following information; where appropriate (the period of observation for the study is described in Section 6):

- AE name or term in standard medical terminology.
- When the AE first occurred (start date and time); SAE start date is defined as the date the AE became serious.
- When the AE stopped (stop date and time or date and time of last observation if ongoing, i.e., recovering or not recovered).
- Severity of the AE.
- Seriousness criteria (hospitalization, death, etc.).
- Action taken with study medication as a result of AE.
- Outcome.
- Investigator's opinion regarding the AE relationship to the study treatments.

Hypoglycemic events and associated signs/symptoms will only be recorded on the hypoglycemic episodes page of the CRF, unless they are SAEs (i.e., a severe episode).

9.3.2.6 Treatment of Adverse Events

AEs that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the reason should be documented in the CRF; this can include temporary interruption of study treatment. The decision about whether the subject may resume the study treatment will be made by the sponsor after consultation with the Investigator and/or medical monitor.

9.3.2.7 Follow-up

Any AE will be followed-up to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate CRF page.

9.3.2.8 Notification

For SAEs, the active reporting period to Mylan, begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including the follow up visit. Should an Investigator be made aware of any SAE occurring any time after the active reporting period, the SAE must be promptly reported to Mylan only in case of reasonable causality (i.e. suspected ADR).

The SAE reporting form is to be completed for all serious adverse events, signed by the Investigator, and emailed or faxed with supporting documentation (e.g., CRFs, hospital records, laboratory reports). Subject identity details (such as but not limited to name or clinic/hospital number) must not be visible on SAE forms or any supporting documentation provided by the Investigator. These should be "blacked out", and replaced with the site and subject's study identification number on every page.

At that time of first notification, the Investigator/designee should provide the following information via the SAE report form:

- Protocol number
- Reporter (study site and Investigator)
- Subject's unique identification number
- Subject's age
- Investigational medicinal product
- Date of first dose of study treatment
- Date of last dose of study treatment, if applicable
- SAE term
- The seriousness criteria that were met
- Investigator's opinion of the relationship to the study treatment
- Severity
- Start and stop (if applicable) of the event (date and time)
- A brief description of the event, outcome to date, and any actions taken
- Concomitant medication at onset of the event
- Relevant past history information
- Relevant laboratory test findings

If the initial notification of an SAE is by telephone, within 24 hours of the initial telephone notification the Investigator must email the written SAE report form that describes the SAE to the Mylan Product Safety and Risk Management department.

The Investigator may be requested by Mylan to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Mylan.

Any missing or additional relevant information concerning the SAE should be provided on a follow-up SAE Report Form. Ensure that any additional information requested by the sponsor or designee about the event, as outlined above (e.g., hospital reports, autopsy report) is provided to the sponsor as soon as it is available.

Sponsor Contact Information for Immediately Reportable Events

All SAEs must be notified within 24 hours by email (preferred) or fax to:

Mylan Product Safety & Risk Management

PV MAIL HUB FOR IMMEDIATE SAFETY REPORTS:

pvclinical@mylan.com

In the event that an electronic acknowledgment is not received within 24 hours for a SAE report submitted by email, please forward the report via fax to +1.304.285.6409.

9.3.2.9 Regulatory Reporting

All AEs, including suspected serious unexpected AEs will be reported in accordance with applicable local regulations. The Investigator is required to comply with applicable regulations (including local law and guidance) regarding notification to her/his regulatory authorities, ethics committees (ECs) and institutions.

Suspected unexpected serious adverse reactions (SUSARs), SAEs and other cases required by the concerned competent authorities will be reported by the sponsor or the sponsor's representative to all concerned parties within the prescribed timeframe. The sponsor or representative will also submit periodic safety reports (for e.g., Development Safety Update Reports) as required by international regulations.

9.4 Special Situations

The Investigator should report any case of pregnancy within 24 hours via the pregnancy report form. Pregnancy exposures must be followed until a final outcome is determined (e.g., parturition, spontaneous or scheduled termination).

9.4.1 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the Investigator immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted throughout the study, as detailed in the schedule of assessments. A woman who is found to be pregnant at the randomization visit (Visit 6 [Week 0]), will be excluded from the study. A woman who becomes pregnant during the study will be immediately discontinued from study treatment. Early discontinuation visit assessments should be performed as soon as possible after learning of the pregnancy. This information should be captured in the pregnancy form and reported to Mylan Product Safety and Risk Management within 24 hours from the time of initial knowledge, even if beyond the closure of the clinical database.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or an SAE. A spontaneous abortion is always considered to be a SAE and will be reported to the sponsor within 24 hours of knowledge of the event.

Elective termination (i.e., without medical reasons) of an uncomplicated pregnancy is considered to be an elective procedure and not an AE, nevertheless, Mylan requests that the outcome (e.g., elective termination) be reported within 24 hours and sent as a follow-up on the Delivery and Infant Follow-up Form).

The Investigator is also responsible for following up the pregnancy at 3 monthly intervals until delivery or termination, informing the sponsor about its outcome.

9.4.2 Overdose, Medication Errors and Other Events

Overdose *per se* of either study treatment or a concomitant medication will not be reported as an AE; unless it is an intentional overdose taken with possible suicidal/self-harming intent. Signs, symptoms, and clinical sequelae associated with intentional overdose are to be recorded on the AE CRF page. Dosing and other medication errors are to be recorded as protocol deviations.

9.5 Abnormal Test Findings

Abnormal laboratory findings per se (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., ECG, X-rays, and vital signs) are not reported as AEs. However, abnormal findings that are deemed **clinically significant** or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as an SAE if they meet the criteria of being serious). Clinically significant abnormal laboratory or other abnormal findings that are detected after study drug administration or that are present at baseline and worsen following the administration of study drug are included as AEs (and SAEs, if serious). The Investigator should exercise his or her medical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Broad guidance for determining whether an abnormal objective test finding should be reported as an AE follows:

- The test result is associated with accompanying symptoms and/or
- The test result requires additional diagnostic testing or medical/surgical intervention and/or
- The test result leads to a change in study dosing or discontinuation from the study, additional concomitant drug treatment, or other therapy; and/or
- The test result is considered to be an AE by the Investigator or sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE.

Any abnormal test result determined by retest to be an error does not require reporting as an AE.

10 REFERENCE LIST

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