MYL-1601D-3001 CLINICAL STUDY PROTOCOL

Protocol Title	A Randomized, Multicenter, Open-Label, Parallel-Group Clinical Study Comparing the Safety and Efficacy of MYL-1601D with NovoLog® in Type 1 Diabetes Mellitus Patients
Product	MYL-1601D (Mylan's Insulin Aspart)
Protocol No.	MYL-1601D-3001
Study Type	Phase 3
Version	5.0
Protocol Date	14 October 2019
IND No.	133571
Sponsor	Mylan GmbH Turmstrasse 24, Tower 4 6312 Steinhausen Switzerland

SIGNATURE PAGE

Protocol Description	MYL-1601D-3001
Product Code	MYL-1601D
Protocol Version	5.0
Protocol Version Date	14 October 2019

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

Date: 14 OCT 2019

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DOCUMENT HISTORY

Document Version, Date	Summary of Changes
Version 5, 14 October 2019	• Update immunogenicity assessment section to include the 3-tier approach: screening, confirmatory and titer assay in line with FDA January 2019 Guidance "Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection". • Updated the statistical sections to include the following: use of tiered approach for determination of ADA status, inclusion of method of imputation in case of missing data, change in the proposed method for tipping point analysis. • Clarified the text in Exclusion Criteria#9, to allow the inclusion of subjects with confirmed inactive viral state in to the study; Exclusion Criteria#14c, to exclude subjects with history of impaired hepatic function based on investigator judgement; • Updated the secondary safety endpoints, to remove the evaluation of change in antibody titer from baseline • Editorial administrative changes implemented throughout the document
Version 4, 04 January 2019	• Change in the Sponsor Address • Inclusion Criteria modified to allow subjects on multiple daily bolus injections of Humalog into study, and to exclude consent by legal representative • Exclusion criteria updated to exclude subjects with history of Marijuana use during 1 year prior to screening • Section on Patient diary and Glucometer updated to include use of diary in place of e-diary and provision of a user manual for the glucometer use to educate and train site personnel and study subjects • Statistical methods updated to use Wald confidence limit method for establishing the confidence interval of the treatment difference in TEAR rate and to use pattern mixture model with the complete-case missing values (CCMV) method (Little 1993) for imputing the missing values. • Secondary safety endpoint modified to remove measurement of Incidence of TEAR for cross-reactive ADA
Version 3, 30 August 2018	• Updated the primary objective, endpoint, immunogenicity assessment and statistical sections to have immunogenicity as assessed by treatment emergent antibody response (TEAR) during the 24-week treatment period as the basis for demonstrating equivalence • Added text to suggest that TEAR rate will not be assessed in isolation but will be part of totality of evidence including changes in HbA1c, FPG, insulin dose, neutralizing antibodies and injection • Editorial and Administrative changes implemented throughout the document

Version 2, 16 July 2018	• Updated the visit schedule to change the frequency of scheduled visits to 4-weekly between Visit 9 and Visit 13 (Treatment Period) as per the feedback from the study sites. Previously the frequency of visits was 3-weekly. • Modified the objectives and endpoints related to Immunogenicity to include the Analysis of impact of Anti-Drug Antibody on pharmacodynamic parameters such as Fasting Plasma Glucose, HbA1c, and insulin dose as suggested by the Agency. Also included Neutralizing Antibody analysis. • Increased the blood volume drawn, to implement additional immunogenicity analysis. • Removal of assessment of estimated Glucose Disposal Rate (eGDR) as a secondary endpoint and at removal of text related to eGDR all the relevant sections of the protocol, as suggested by the Agency. • Modified the Statistical section to use the analysis of covariance (ANCOVA) model for analysis of study endpoints, as suggested by the Agency. • Modified statistical sections to include multiple imputations to fill in missing values for HbA1c prior to running the ANCOVA model, to minimize any bias due to missing data. • Editorial Administrative changes implemented throughout the document, including clarification on use of e-diary, and medical monitoring support with its contact details.

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Multicenter, Open-Label, Parallel-Group Clinical Study Comparing the Safety and Efficacy of MYL-1601D with NovoLog® in Type 1 Diabetes Mellitus Patients.
Background and Rationale	Mylan's Insulin Aspart, MYL-1601D, injection [rDNA origin] is a rapid-acting human insulin analog used to lower blood glucose. MYL-1601D is homologous with regular human insulin except for a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing Pichia pastoris (yeast). The current marketed US Insulin Aspart injection, NovoLog®, is homologous with regular human insulin except for a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing Saccharomyces cerevisiae (baker's yeast) as the production organism. MYL-1601D is being developed as a biosimilar to US-licensed NovoLog® and EU-approved NovoRapid®. The aim of this trial is to demonstrate the equivalence in the safety and efficacy profile between MYL-1601D and NovoLog® in patients with T1DM. The trial design is an open-label since the two products have distinct packaging. To avoid any bias in the evaluation of the critical endpoints, immunogenicity, glycosylated hemoglobin (HbA1c) and Fasting plasma glucose (FPG) will be analyzed at a central laboratory in a blinded manner. In addition, study personnel (Sponsor and select CRO staff) will be blinded to the randomized assigned treatment arms.
Primary Objectives	To demonstrate that immunogenicity as assessed by treatment emergent antibody response (TEAR) rate with MYL-1601D is equivalent to that of NovoLog® during 24-week treatment. The TEAR rate will not be assessed in isolation but will be part of totality of evidence including changes in HbA1c, FPG, insulin dose, neutralizing antibodies and injection site reactions to ensure that changes in TEAR rate, if any, are clinically meaningful.
Primary endpoints	The TEAR rate during 24-week treatment period is the primary endpoint for this study. TEAR is defined as either one of the following: 1) subjects who are anti-drug antibody (ADA) negative at baseline and become positive at any timepoint post baseline 2) Subjects who are ADA positive at baseline and demonstrate 4-fold increase in titer values at any timepoint post baseline visit.
Methodology and treatments	This is a multicenter, open-label, randomized, parallel-group phase 3 study in subjects with T1DM comparing the safety and efficacy of MYL-1601D with NovoLog®. After up to 3-week screening period, all subjects will be titrated on NovoLog® during a 4-week run-in period, and will be shifted from their current basal insulin to study insulin Lantus®. After run-in period, subjects will be randomized; one group will receive MYL-1601D, while the other group will receive NovoLog® for 24 weeks. A follow-up visit, via telephone call, will be scheduled 4 weeks after last dose of MYL-1601D.

	The study will be conducted at approximately 200 sites in the United States (US).
Inclusion/ exclusion criteria	**Inclusion criteria** 1. Written and signed informed consent needs to be provided by subjects before starting any protocol-specific procedures. 2. Male and female subjects between the ages of 18 to 65 years, both ages inclusive. 3. Clinical diagnosis of type 1 diabetes mellitus for at least 6 months prior to screening. 4. Stable dose of once daily basal Lantus® or Toujeo® injection and multiple daily bolus NovoLog® or Humalog® injections for at least 3 months at screening. 5. Body mass index (BMI) of 18.5 to 35.0 kg/m^2 at screening (both values inclusive). 6. Stable weight, with no more than 5 kg gain or loss in the 3 months prior to screening (collected by subject interview during medical history). 7. Glycosylated hemoglobin (HbA1c) 6.5-10.0% at screening. 8. Hemoglobin ≥ 10.0 g/dL at screening. 9. Subject has the capability of communicating appropriately with the Investigator. 10. Subject is able and willing to comply with the requirements of the study protocol including the 7-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. 11. 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 2 years or use of approved or experimental biosimilar product or any experimental insulin at any time prior to study entry including MYL-1501D. 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 (However, Subjects with confirmed inactive viral state can be included). 10. History of drug abuse, marijuana use, or alcohol dependence 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 hyperthyroidism or hypothyroidism (subjects can be included if these conditions are controlled with thyroid hormones or anti-thyroid drugs). c. History of impaired hepatic function which is seen in the screening laboratory test and is judged by the investigator to be clinically significant - 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, and have not experienced a major depressive episode 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 total 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 3 months, 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 screening.

Sample size	Approximately 500 subjects with type 1 diabetes will participate in this trial. The sample size estimation is based on primary objective – "to demonstrate that immunogenicity as assessed by TEAR rate with MYL-1601D is equivalent to that of NovoLog® during 24-week treatment" as recommended by the FDA. The 80% power will be achieved with 250 subjects per treatment arm to demonstrate that 90% confidence interval of treatment difference (MYL-1601D minus NovoLog®) is within prespecified ± margin (Table 5).
Statistical Methods	The 90% confidence interval of treatment difference in TEAR rate will be established using Wald confidence limit method. TEAR rate with ADA of MYL-1601D is equivalent to that of NovoLog® during 24-week treatment if 90% confidence interval of treatment difference is within pre-specified margin, the specific margin will be determined by final reference drug TEAR rate as recommended by the agency (Table 5). For secondary continuous variables, a mixed model repeated measures (MMRM)-effects model will be performed.

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LIST OF COMMONLY USED ABBREVIATIONS

ADA	Anti-Drug Antibody
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
FPG	Fasting Plasma Glucose
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
IWRS	Interactive Web Response System
ITT	Intent to treat
IU	International Unit
kg	Kilogram
LFT	Liver Function Test
LOCF	Last Observation Carried Forward

MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Milliliter
MMRM	Mixed Model Repeated Measures
PP	Per Protocol
PSRM	Product Safety and Risk Management
REML	Restricted maximum likelihood
RFT	Renal Function Test
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
TEAR	Treatment Emergent Antibody Response
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

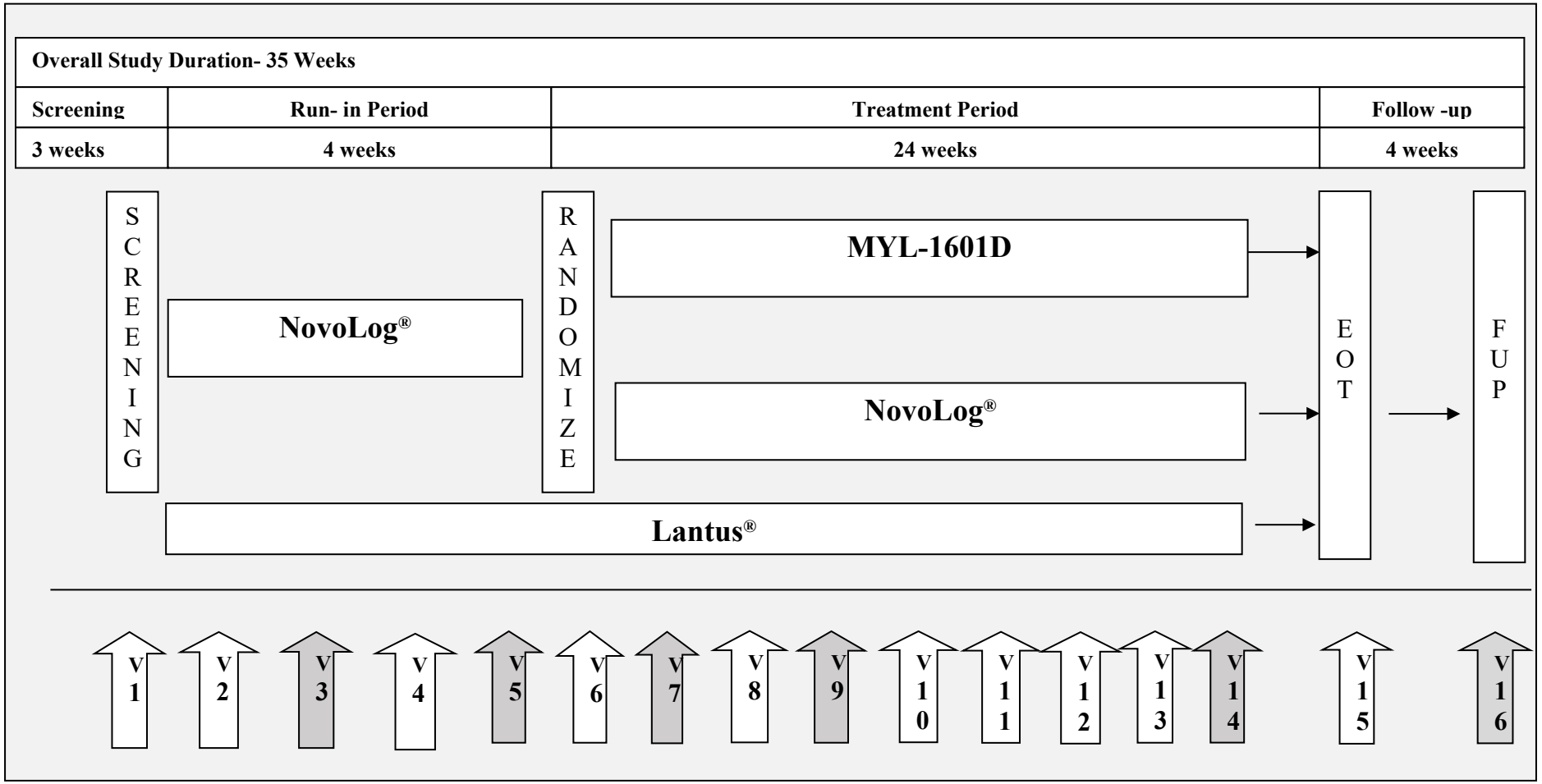

Table 1: Study Schedule of Activities

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	V15 (EOT) [9]	V16 (FU)
Study Week	-7 to -4	-4	-3	-2	-1	0	1	2	4	8	12	16	20	22	24	28
Study Days	-49 to -28	-28±3	-21±3	-14±3	-7±3	0±3	7±3	14±3	28±3	56±7	84±7	112±7	140±7	154±7	168±7	196±7
Informed Consent	x															
Inclusion/Exclusion Criteria Review	x					x										
History of previous insulin usage	x															
Dilated Ophthalmoscopy / retinal photography (if not done the last 6 months)	x															
Standard-of-care specifics [2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Age, Gender, Height, Race	x															
Body Weight and BMI [10]	x	x		x		x		x	x	x	x	x	x		x	
Pregnancy Test [3]	x	x				x			x	x	x	x	x		x	
Medical History and concomitant illness	x															
Concomitant Medications	x	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	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	V15 (EOT) [9]	V16 (FU)
Study Week	-7 to -4	-4	-3	-2	-1	0	1	2	4	8	12	16	20	22	24	28
Study Days	-49 to -28	-28±3	-21±3	-14±3	-7±3	0±3	7±3	14±3	28±3	56±7	84±7	112±7	140±7	154±7	168±7	196±7
Physical examination	x					x									x	
12-lead ECG (supine)	x														x	
Randomization						x [7]										
Record AEs and SAEs (including local and systemic allergic reactions) and hypoglycemic events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record device complaint			x	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	
Rescue criterion evaluation [5]												x				
Fasting C-peptide, HIV, HBsAg, HCVAb	x															
Sampling for hematology, blood chemistry and urinalysis [4]	x					x									x	
Fasting lipid profile						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	V15 (EOT) [9]	V16 (FU)
Study Week	-7 to -4	-4	-3	-2	-1	0	1	2	4	8	12	16	20	22	24	28
Study Days	-49 to -28	-28±3	-21±3	-14±3	-7±3	0±3	7±3	14±3	28±3	56±7	84±7	112±7	140±7	154±7	168±7	196±7
Sampling for immunogenicity [8]	x					x		x	x	x	x	x	x		x	
Review diary, 7-point SMBG Profile and dose collection performed in the week before the visit [6]				x		x		x	x	x	x	x	x		x	
Dose review of MYL-1601D, NovoLog® and Lantus® and dose adjust/instruction		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Dispense study medication and ancillary supplies		x				x			x	x	x	x	x			
Drug Accountability and Compliance				x		x		x	x	x	x	x	x		x	
Dispense subject diary		x		x		x		x	x	x	x	x	x			

1. Visits 3, 5, 7, 14 and 16 are telephone contacts/visits, in case required an actual site visit is possible *(*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 childbearing potential will be done during screening and randomization visits (V1 and V6). During subsequent visits urine pregnancy test will be done, any positive urine test needs to be confirmed with serum test. At the randomization visit, both urine and serum pregnancy tests will be done; subject can be enrolled only if the urine pregnancy test is negative until serum result is provided.
4. 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 and the Investigator deems it clinically significant and requests further evaluation.
5. Rescue criterion is evaluated on V12/Week 16 based on HbA1c measurement at V11/Week 12. Sites are required to receive the V11/Week 12 results prior to V12/Week 16 subject visit to enable Investigator to take decision on future steps.

6. The 7-point SMBG profile recorded via glucometer and recorded by the subject in the diary, measurement will be performed by the subject at home on 3 days (of which 2 days are consecutive) in the week before the visit.
7. Prior to randomization, Investigator is required to re-confirm subject eligibility to the study based on the data collected during the screening period, including the labs values recorded during screening.
8. Immunogenicity samples: At Visits 1, 6, 8, 9, 10, 11, 12, 13 and 15. At each visit, five blood samples of 5 mL each (25 ml per visit) will be drawn for ADA and NAb.
9. V15 is regard as Early Termination from Treatment visit or Study End of Treatment visit. In case the subject discontinues treatment early, the site should explain the importance of data collection and make every effort to retain the subject, perform the remaining visits, off study treatment, per the SCHEDULE OF ACTIVITIES, up to the completion of Week 28/Follow-up call.
10. BMI is calculated at screening visit, randomization visit, week 12 and week 24.

2 INTRODUCTION

2.1 Indication

MYL-1601D is being developed as a follow-on biologic (US terminology) to the US-licensed NovoLog®.

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 (de Graaff LC et al, 2007). 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 and other trials (Reichard P et al, 1993) 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 (American Diabetes Association 2019).

Different insulin preparations are available for management of bolus insulin requirements, including; Apidra® (glulisine), Humalog® (lispro), NovoLog® (aspart). Rapid-acting insulin analogs have proven efficacy and offer good glucose control via regimen of 1 to 3 dose/injections per day. Insulin aspart is a rapid-acting insulin analogue administered once to three times a day to cover bolus insulin requirements per day.

MYL-1601D (Mylan insulin aspart) is a rapid-acting human insulin analog. The primary activity of insulin aspart is the regulation of glucose metabolism, it binds to the insulin receptors on muscle and fat cells, and it leads to a decrease in blood glucose by facilitating the cellular uptake of glucose while simultaneously inhibiting the output of glucose from the liver. MYL-1601D is produced by recombinant DNA technology utilizing *Pichia pastoris* (yeast). The primary structure is identical to endogenous insulin, except for replacement of a single proline amino acid at position 28 in the C-terminal area of the insulin B-chain with an aspartic acid residue. This substitution weakens the natural tendency towards self-association between insulin monomers, thereby inhibiting aggregation into hexamers and accelerating absorption after sub-cutaneous injection.

The aim of this trial is to demonstrate the equivalence in the safety and efficacy profile between MYL-1601D and NovoLog® in patients with T1DM with primary focus on assessment of immunogenicity and its potential clinical impact on safety and efficacy.

In case of prandial insulins like aspart, PK-PD study using an euglycemic clamp is a very sensitive and robust tool to assess potential differences in efficacy between biosimilar products versus traditional endpoints like HbA1c. This approach of using PD parameters

from euglycemic clamp as a key surrogate efficacy measure has been acknowledged by both FDA and EMA. In this context, the current study in T1DM patients is primarily aimed at addressing residual uncertainty with specific focus on assessment of immunogenicity.

Systemic assessment of immunogenicity is a relatively new area and limited information and approaches are available for analyzing these data. Furthermore, the immunogenicity profile is highly dependent on the ADA assay format and thus data from one study cannot be easily extrapolated to another study especially with regards to incidence rates. The problem is further compounded by the fact that limited data is available from the innovator NovoLog® studies.

Despite these limitations based on feedback from FDA, Mylan is proposing to use differences in treatment emergent antibody response (TEAR) rate as the primary endpoint for this study. However, given that TEAR rate is not available from innovator clinical studies and that the assay formats might be different, formal hypothesis testing to demonstrate that the incidence of specific end point falls within a predetermined equivalence margin is going to be challenging and a generalized equivalence margin approach suggested by FDA is proposed in Table 5.

Furthermore, as discussed extensively with the agency, the clinical relevance of TEAR rate is still not confirmed and although the TEAR rate is the primary statistical endpoint, it will not be assessed in isolation but will be part of totality of evidence including changes in HbA1c, FPG, insulin dose, neutralizing antibodies and injection site reactions to ensure that changes in TEAR rate, if any, are clinically correlated and meaningful.

The trial design is an open-label since the two products have distinct packaging. To avoid any bias in the evaluation of the critical endpoints, immunogenicity, glycosylated hemoglobin (HbA1c) and FPG will be analyzed at a central laboratory in a blinded manner. In addition, study personnel (Sponsor and CRO) will be blinded to the randomized assigned treatment arms, this will be documented to ensure transparency and proper study conduct.

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 multiple daily insulin injections bolus NovoLog® or Humalog® and once daily basal Lantus® or Toujeo® for at least 3 months prior to screening will be included.

During the 4-week run-in period with NovoLog® and Lantus®, the dose of insulin will be titrated (if required) to ensure diabetes control and patients who are receiving basal insulin other than Lantus® will be switched to this basal-bolus combination (Lantus®-NovoLog®). 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. The run-in period also serves as an approach to single transition, wherein all patients entering the run-in period will be receiving NovoLog® for 4 weeks and following randomization to the treatment period patients will receive either NovoLog® or MYL-1601D allowing for assessment of switch from reference, NovoLog®, to the test product, MYL-1601D. A 24-week treatment period is an adequate period to detect differences in HbA1c and safety parameters of the treatment arms (EMEA 2006).

Dosing with NovoLog® during run-in period, and MYL-1601D and NovoLog® during treatment period will be guided by self-monitored blood glucose (SMBG)-based glucose

level assessments and by the Sponsor titration dose review team as detailed in the insulin monitoring titration plan.

Rescue criteria based on HbA1c are defined based HbA1c measurement performed on V11/week 12, 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, 4 weeks after the end of treatment, will ensure the safety of all subjects after they stop the study medication and return to receiving market approved medications at the discretion of their physician.

Complete information for the study medication can be found in MYL-1601D Investigator's Brochure (IB).

2.2.1 Rationale for Dose Selection

Only patients who have been on a stable multiple daily insulin injections dose of NovoLog® or Humalog® and once daily basal Lantus® or Toujeo® for at least 3 months prior to screening will be included in the study. If required, patient dose should be adjusted during the 4-week run-in period to stabilize the patient dose. During the treatment period, dose adjustment should be avoided but it is permitted to ensure patient's stable state and safety.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objectives

To demonstrate that immunogenicity as assessed by treatment emergent antibody response (TEAR) rate with MYL-1601D is equivalent to that of NovoLog® during 24-week treatment.

The TEAR rate will not be assessed in isolation but will be part of totality of evidence including changes in HbA1c, FPG, insulin dose, neutralizing antibodies and injection site reactions to ensure that changes in TEAR rate, if any, are clinically meaningful.

3.1.2 Other objectives

To compare MYL-1601D to NovoLog® administered in combination with Lantus®, with respect to:

- Immunogenicity assessments: visits TEAR assessments, incidences of Anti-Drug Antibody (ADA), positive insulin cross-reactive ADA, and positive Neutralizing Antibody (NAb)
- Analysis of impact of ADA on pharmacodynamic (PD) parameters such as FPG, HbA1c, and insulin dose.
- Incidence and rate of hypoglycemic events
- Occurrence of local reactions, systemic reactions and other adverse events
- Safety related to hypersensitivity and immune mediated adverse events (subgroup analysis)
- Change in HbA1c from baseline
- Change in fasting plasma glucose (FPG) from baseline
- Change in prandial, basal, and total daily insulin dose per unit body weight (U/kg) from baseline
- Change in 7-point SMBG profile from baseline
- Device-related safety assessment

3.2 Endpoints

3.2.1 Primary Endpoints

The TEAR rate during 24-week treatment period is the primary endpoint for this study.

TEAR is defined as either one of the following:

1) Subjects who are ADA negative at baseline and become positive at any timepoint post baseline

2) Subjects who are ADA positive at baseline and demonstrate 4-fold increase in titer values at any timepoint post baseline visit.

3.2.2 Secondary Endpoints

The secondary endpoint points are change from baseline to week 24.

3.2.2.1 Efficacy

- Change in HbA1c from baseline
- Change in fasting plasma glucose from baseline
- Change in prandial, basal and total daily insulin dose per unit body weight (U/kg) from baseline
- Change in 7-point SMBG profile from baseline

3.2.2.2 Safety

- Incidence of positive antibody response and NAb
- Impact of ADA on PD parameters, such as FPG, HbA1c, and insulin dose.
- 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 (includes injection site reaction), systemic reactions.
- Incidence of hypersensitivity and immune mediated adverse events.
- Incidence of device-related safety assessment.

4 STUDY POPULATION

4.1 Study Population

A total of 500 subjects with T1DM are planned to be randomized in this study, to receive MYL-1601D or NovoLog® 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 before starting any protocol-specific procedures.

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

3. Clinical diagnosis of type 1 diabetes mellitus for at least 6 months or more prior to screening.

4. Stable dose of once daily basal Lantus® or Toujeo® injection and multiple daily bolus NovoLog® or Humalog® injections for at least 3 months at screening.

5. Body mass index (BMI) of 18.5 to 35.0 kg/m^2 at screening (both values inclusive).

6. Stable weight, with no more than 5 kg gain or loss in the 3 months prior to screening (collected by subject interview during medical history).

7. Glycosylated hemoglobin (HbA1c) 6.5-10.0 % at screening.

8. Hemoglobin ≥ 10.0 g/dL at screening.

9. Subject has the capability of communicating appropriately with the Investigator.

10. Subject is able and willing to comply with the requirements of the study protocol including the 7-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.

11. 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 2 years or use of approved or experimental biosimilar product or any experimental insulin at any time prior to study entry including MYL-1501D.

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 (However, Subjects with confirmed inactive viral state can be included).

10. History of drug abuse, marijuana use, or alcohol dependence 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 hyperthyroidism or hypothyroidism (subjects can be included if these conditions are controlled with thyroid hormones or anti-thyroid drugs).

    c. History of impaired hepatic function which is seen in the screening laboratory test and is judged by the investigator to be clinically significant - 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, and have not experienced a major depressive episode 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 total 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 3 months, 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 Early Termination or Discontinuation

Subjects can decide to discontinue entirely from the study at any time for any reason, this is documented as withdrawal of consent. Subjects can decide to discontinue from the study treatment at any time for any reason, but may choose to remain in the study for off-treatment study visits. Subjects can also be discontinued from the study or discontinued from the study treatment due to Investigator or Sponsor decision as detailed below.

The Sponsor or their representative must be notified by the Investigator as soon as possible, and prior to the early termination visit, on the decision to discontinue the subject from the study or from study treatment and provide detailed information on the reason/event.

In case of discontinuation of the subject from the study, an early termination visit (outlined as an End of Treatment visit in the Schedule of Activities) is required immediately and the site must complete the End of Study eCRF data. In case of the discontinuation of the subject from the study treatment, the subject is required to complete the End of Treatment visit, switch to marketed treatment (both basal and bolus treatments) and agree to proceed with the scheduled visits/activities.

The reason for discontinuation should be established based on the following reasons and recorded.

The following are reasons for discontinuation:

1. Withdrawal of consent.

2. For female subjects, diagnosis of pregnancy or stated intention to become pregnant. In this case subjects should be discontinued from the study (early termination visit is done immediately). 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. In this case subjects can be discontinued from the study (early termination visit is done immediately) or discontinued from the study treatment and continue with the study visits and procedures with marketed treatment (no need to perform early termination visit as subject proceed with the scheduled visits). The site should request the subject consent to follow-up as per the SCHEDULE OF ACTIVITIES until the Week 28 (Follow-up visit).

4. At the Investigator's discretion (following discussion with the Sponsor medical monitor), in certain situations such as lack of compliance, significant illness, hospitalization for surgery, or an SAE. In this case subjects can be discontinued from the study (early termination visit is done immediately) or discontinued from the study treatment and continue with the study visits and procedures with marketed treatment (no need to perform early termination visit as subject proceed with the scheduled visits).

5. Sponsor terminate the study due to safety issues. In this case subjects should be discontinued from the study (early termination visit is done immediately).

Subjects who decide to discontinue from treatment and agree to remain in the study, on marketed treatment, are required to adhere to the study protocol, thus perform all activities and procedures such as SMBG measurements, completing diary entries, participating in their regularly scheduled study visits for completion of all assessments and procedures as outlined in the Schedule of Activities until the Week 28 (Follow-up visit).

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.

The site should explain the subject the importance of data collection and make every effort to consent the subject to continue follow up per the SCHEDULE OF ACTIVITIES until Week 28 (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 childbearing 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 urine positive test, serum test will be done to confirm the result, following the subject will be withdrawn from the study (or will not enter the study if during screening).

5 STUDY DRUG

5.1 Investigational Drug

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

MYL-1601D Product (100 U/mL)

or

FlexPen® NovoLog® (100 U/mL) US Listed Drug

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

- During the run-in period, all subjects will receive FlexPen® NovoLog® manufactured by Novo-Nordisk for the US (US listed drug), 100 U/mL.
- All subjects will receive Lantus® SoloSTAR® pen (insulin glargine injection, 100 U/mL), manufactured by Sanofi-Aventis, throughout the study.

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

All drugs will be packaged and labeled according to US legal requirements.

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 randomization 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 FlexPen® NovoLog® from Novo-Nordisk (US listed drug) 100 U/mL until randomization. In addition, all patients will be shifted from their current basal insulin to Lantus® SoloSTAR® at the start of the run-in period, and will continue this for the complete study duration. The doses of NovoLog® and Lantus® will be titrated (if required) during the run-in period to ensure diabetes control.

During the **Treatment period,** all patients will receive one of the following treatments:

- MYL-1601D or FlexPen® NovoLog® to be taken at meal time. 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.
- Once daily Lantus® SoloSTAR® (insulin glargine injection, 100 U/mL), manufactured by Sanofi-Aventis.

In the event of any dosing errors, medication error or device complaint, the CRO contact person and/or CRO medical monitor and/or Mylan study contact person should be contacted and 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 labeled 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 or designee.

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 IWRS. A manual containing complete instructions for Web access and use will be provided to each site prior to study start. The 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 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

The trial design is open-label since the two products, MYL-1601D and NovoLog®, have distinct packaging. To avoid any bias in the evaluation of the critical endpoints, a blinded analysis of immunogenicity and other parameters such as HbA1c and FPG is planned. In addition, the majority of the study personnel (Sponsor and select CRO staff) will be blinded to the randomized assigned treatment arms and this will be documented, listing the Sponsor and CRO personnel who are unblinded to ensure transparency and proper study conduct.

As all Investigators and sites staff are not blinded to treatment, no process required for breaking the blind.

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 (except for insulin) 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 (MYL-1601D, NovoLog® and Lantus®), other insulins / other 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. disopyramide 4. fibrates 5. fluoxetine 6. monoamine oxidase inhibitors 7. propoxyphene 8. pentoxifylline 9. somatostatin analogs 10. bromergocryptine (bromocryptine) 11. 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). 15. marijuana

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 4.2.3).

5.7 Rescue Criterion

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".

At the week 16 (Visit 12) study visit, if the subject meets the rescue criterion above, the Investigator can decide to proceed with one of the following options;

1) continue the study with no drug change
2) continue the study and adjust the dose of the study treatment
3) discontinue from the study treatment and switch to study NovoLog® if the subject is assigned to MYL-1601D
4) discontinue from the study treatment if the subject is already assigned to NovoLog® and switch to marketed treatment (both basal and bolus treatments)
5) early termination from 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 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 visits 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 early termination 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 35 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 -7 to Week -4])

Subjects will commence screening procedures within up to 7 weeks prior to randomization, to confirm that they meet the selection criteria for the study. If the time between screening procedures and the run-in period exceeds 3 weeks, due to unexpected delays, drop out, or any other reason, the subject can be rescreened one time based on discussion between the site or designee and with Mylan personnel. In case re-screening is agreed, the subject will need to be re-consented and assigned a new SID via IWRS. If re-screening occurs, the reason and approval needs to be clearly documented within the site file.

The following will be completed 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.
- Check eligibility criteria.
- Record detailed history of all previous insulin use (as far as the patient can remember).
- 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 American Diabetes Association 2019 guidelines, self-management of diabetes and life-style modifications with the subject.
- Record demographic details (age, gender, height, 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).
- 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
    - Immunogenicity analysis
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events which occur after time of informed consent signature.

After all assessments have been performed, the Investigator will assess the results for compliance with the inclusion and exclusion criteria. Immunogenicity results are not needed for eligibility. 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.

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 American Diabetes Association 2019 guidelines, self-management of diabetes and life-style modifications with the subject.
- Record body weight.
- 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 urine sample for pregnancy test.
- Dispense subject diary and glucometer to the subject and provide information regarding the diary completion requirements and necessary glucose measurements provided, and the use and requirements of the glucometer.
- Review current dosing of NovoLog® and Lantus® and if necessary provide new dosing instructions and document the new dose and reason for change (specifically for change from basal Toujeo® to Lantus®).
- 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 are telephone contacts/visits, in case required an actual site visit is possible. 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 the subject diary and 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 American Diabetes Association 2019 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 complaint.
- Review current dosing of NovoLog® and Lantus® 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 American Diabetes Association 2019 guidelines, self-management of diabetes and life-style modifications with the subject.
- Record body weight.
- 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 complaint.
- Review the results of 7-point SMBG measurements, performed on 3 days during the week prior visit for the last two weeks.
- Review current dosing of NovoLog® and Lantus® 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 and 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:

- Re-check and re-confirm the eligibility criteria.
- Perform randomization.
- Discuss and check compliance to standard of care specifics as per American Diabetes Association 2019 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.
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic events since the previous visit.
- Record device complaint.
- 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)
- Review the results of 7-point SMBG measurements, performed on 3 days during the week prior to the visit for the last two weeks.
- Review current dosing of NovoLog® and Lantus® and only if necessary provide new dosing instructions and document the new dose and reason for change.
- Dispense study medication MYL-1601D or NovoLog® and Lantus®.
- Perform drug accountability and check for treatment compliance.
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided.

6.3.2 Visit 7 (Week 1), Visit 14 (Week 22)

These visits are telephone contacts/visits, in case required an actual site visit is possible. 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 and 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 American Diabetes Association 2019 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 complaint.
- Review current dosing of MYL-1601D or NovoLog® and Lantus® and only if necessary provide new dosing instructions and document the new dose and reason for change.
- At Visit 14 (Week 22), remind subject of the date and time for Visit 15 (Week 24) .

6.3.3 Visit 8 (Week 2), Visit 9 (Week 4), Visit 10 (Week 8), Visit 11 (Week 12), Visit 12 (Week 16), Visit 13 (Week 20)

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

- Discuss and check compliance to standard of care specifics as per American Diabetes Association 2019 guidelines, self-management of diabetes and life-style modifications with the subject.
- Record body weight and calculate BMI only at Visit 11 (Week 12).
- 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 complaint.
- 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), except for Visit 8.

  - Fasting plasma glucose, except for Visit 8.
  - Immunogenicity analysis (collect blood sample prior to study drug administration).
  - HbA1c done only at Visit 11/Week 12.
- Assess rescue criterion and record decision in case positive at Visit 12/Week 16.
- Review the 7-point SMBG measurements, performed on 3 days during the week prior to the visit.
- Review current dosing of MYL-1601D or NovoLog® and Lantus® and if necessary provide new dosing instructions and document the new dose and reason for change.
- Review subject diary and provide information regarding the completion requirements and necessary glucose measurements provided.
- Dispense study medication MYL-1601D or NovoLog® and Lantus®, except for Visit 8.
- Perform drug accountability and check for treatment compliance.
- Dispense diary.

6.3.4 Visit 15/Early Termination from Treatment/Study Termination/ End of Treatment (EOT, Week 24)

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

- Discuss and check compliance to standard of care specifics as per American Diabetes Association 2019 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 complaint.
- Collect blood and urine samples for the following laboratory assessments:
  - Urine pregnancy test for women of childbearing potential
  - Fasting plasma glucose
  - HbA1c
  - Hematology
  - Blood chemistry
  - Urine analysis
  - Fasting lipid profile
  - Immunogenicity analysis (collect blood sample prior to study drug administration)
- Review diary, 7-point SMBG measurements, performed on 3 days during the week prior to the visit.
- Review current dosing of MYL-1601D or NovoLog® and Lantus® .
- Subject should be instructed on the switched to the marketed products; dosing and administration instructions.

- Collect all study materials for last study treatment visit (in case of Early Termination from Treatment/End of Treatment). In case subject is discontinued from the study treatment but agrees to continue and perform the study visits and procedures the materials will be kept until the subject last visit to the site which is visit 15.
- Perform drug accountability and check for treatment compliance.

6.3.5 Early Termination

Subjects can decide to discontinue entirely from the study at any time for any reason, this is documented as withdrawal of consent. Subjects can decide to discontinue from the study treatment at any time for any reason, but may choose to remain in the study for off-treatment study visits. Subjects can also be discontinued from the study or discontinued from the study treatment due to Investigator or Sponsor decision as detailed below.

The Sponsor or their representative must be notified by the Investigator as soon as possible, and prior to the early termination visit, on the decision to discontinue the subject from the study or from study treatment and provide detailed information on the reason/event.

In case of discontinuation of the subject from the study, a study termination visit (outlined as an End of Treatment visit in the Schedule of Activities) is required immediately and the site must complete the End of Study eCRF data. In case of the discontinuation of the subject from the study treatment, the subject is required to complete the End of Treatment visit, switch to marketed treatment (both basal and bolus treatments) and agree to proceed with the scheduled visits/activities.

The reason for discontinuation should be established based on the criteria for discontinuation/early termination as stated in Section 4.2.3.

Subjects who decide to discontinue from treatment and agree to remain in the study, on marketed treatment, are required to adhere to the study protocol, thus perform all activities and procedures such as SMBG measurements, completing diary entries, participating in their regularly scheduled study visits for completion of all assessments and procedures as outlined in the Schedule of Activities until the Week 28 (Follow-up visit).

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.

The site should explain the subject the importance of data collection and make every effort to consent the subject to continue follow up per the SCHEDULE OF ACTIVITIES until Week 28 (Follow-up visit).

6.4 Visit 16 Follow up (Week 28) (telephone call)

- Discuss and check compliance to standard of care specifics as per American Diabetes Association 2019 guidelines, self-management of diabetes and life-style modifications with the subject.
- Record AEs, SAEs, local and systemic allergic reactions and hypoglycemic episodes
- 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 375 mL.

Table 3: Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times		Total Volume (mL)
		Screening	Study Period	
Safety Labs	30	1	2	90
FPG, HbA1c	5	2	10	60
Anti-drug antibody (ADA) [1]	10	1	8	90
Neutralizing antibody (NAb) [2]	5	1	8	45
Supplemental Immunogenicity[3]	10	1	8	90
TOTAL				**375**

[1] Blood samples (2 x 5 mL) will be drawn into serum separator tubes (SST).
[2] Blood samples (1 x 5 mL) will be drawn into serum separator tubes (SST).
[3] Blood samples (2 x 5 mL) 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 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 fulfills ICH criteria for seriousness (life-threatening, hospitalization etc.) or represent important medical events based on Investigator's judgment should also be reported to the 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 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 in the diary and reported 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 Section 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[0]	Urine/Serum 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 the 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 the 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.

Per schedule of activities in Table 1 and Section 6, study conduct, samples are taken under fasting conditions, as described in the laboratory manual. Patients are required to adhere to those requirements/instruction.

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 (5 mL each) will be taken into serum separator tubes at each time point as outlined in Table 3. At Visits 1, 6, 8, 9, 10, 11, 12, 13 and 15, five (5) blood samples of 5 mL each (25 mL total volume) will be drawn. The blood samples will be taken pre-dose 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 ADA against insulin aspart using the approach outlined below. One sample will be used to determine the presence of NAbs against insulin aspart for samples that are ADA positive. Two samples will be collected and stored in reserve for potential supplemental immunogenicity testing and/or characterization including titer assessment if needed. 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, processing, and storage instructions will be detailed in a separate laboratory manual.

A conventional radioimmunoprecipitation assay (RIPA) will be employed for the assessment of ADA 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-1601D tracer under conditions specified for each tier:

Screening Assay (Tier 1):
- RIPA Assay buffer only

Confirmatory Assay (Tier 2):
- RIPA Assay buffer only
- RIPA Assay buffer with excess unlabelled MYL-1601D
- RIPA Assay buffer with excess unlabelled Human Insulin
- RIPA Assay buffer with excess unlabelled NovoLog

Titer assay (Tier 3)
- RIPA Assay buffer only (multiple serial dilutions of the sample)

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).

In keeping with the multi-tiered sample analysis recommendations for immunogenicity testing from published white papers (Mire-Sluis AR et al, 2004; Shankar G et al, 2008), and

current regulatory guidance (FDA 2019, EMA 2017), the assay design will employ a screening tier (no inhibition), confirmatory tier (competitive inhibition with excess drug), characterization tier (competitive inhibition with excess human insulin and excess NovoLog®) and titration tier.

All samples will be subjected to an initial screening assay (Tier 1), and those with %B/T values greater than or equal to a run-specific screening cut point will be scored as putative ADA positives.

Screen positive samples would then undergo the confirmatory assay (Tier 2), and samples exhibiting percentage inhibition greater than the confirmatory cut point will be scored as confirmed positive. The cut-point for the screening assay will be based on the %B/T response using normal human serum from treatment naïve individuals and use a 5% false positive error rate. The confirmatory cut points will be determined for both ADA and insulin cross-reactive ADA based on the % inhibition of tracer binding using excess MYL-1601D and human insulin, respectively. Each confirmatory cut-point will be determined using normal human serum from treatment naïve individuals and employ a 1% false positive error rate. The percent inhibition determined using NovoLog as inhibitor would be reported for comparison purposes.

All confirmed positive samples will be evaluated for titer (Tier 3) by serially diluting the samples (2-fold dilution steps) and estimating the titer as the interpolated dilution at the run specific titer cut point (determined from the screening data using normal human serum from treatment naïve individuals at 0.1% false positive error rate). In addition, all samples identified as ADA positive will be further evaluated for neutralizing antibodies using a separate cell-based assay.

The labeled drug product (^{125}I-MYL-1601D) is used as the capture reagent in the RIPA, which allows antibodies that arise from any insulin aspart epitope to be bound and detected. The specificity of capture reagent binding is confirmed by treatment with excess unlabeled MYL-1601D, which will interrupt binding for any of the insulin aspart epitopes. Because this assessment theoretically detects all antibodies that may arise due to drug exposure, it will be used to determine patient sample ADA status.

Since endogenous human insulin possesses close sequence homology to insulin aspart, the ADA generated upon drug exposure may also cross react with human insulin. The degree of cross reactivity will be determined by testing the sample in the presences of excess human insulin. ADA that develop against epitopes common to both insulin aspart and human insulin will be inhibited from binding to the capture reagent.

All samples designated for immunogenicity evaluation will be tested in a blinded manner. The ADA and NAb analysis methodologies will be fully validated at Celerion Switzerland AG (Zurich, CH) and Cirion BioPharma Research Inc. (Quebec, CA), respectively, followed by sample analysis.

6.5.2.5 Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in Section 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 Section 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 Diary and Glucometer

All subjects will receive a diary and blood glucose monitoring (glucometer) device at Visit 2/Week -4. The glucometer device will be used by the subject at home to monitor blood glucose and the diary will be used to record the 7-point SMBGs. The Investigator or designee will train subjects on how to use the glucometer and how to record the values and required information in the diary. A user manual for the glucometer is provided to each site as a tool to educate and train both site personnel and study subjects.

6.5.2.8 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 15 (EOT).

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

Approximately 500 subjects with type 1 diabetes will participate in this trial. The sample size estimation is based on primary objective - to demonstrate that immunogenicity as assessed by TEAR rate with MYL-1601D is equivalent to that of NovoLog® during 24-week treatment. The 80% power will be achieved with 250 subjects per treatment arm to demonstrate that 90% confidence interval of treatment difference (MYL-1601D minus NovoLog®) is within prespecified ±margin (Table 5). (Chow SC et al, 2002; Chow S-C et al, 2003). The pre-specified equivalent margin is dependent on the final rate of NovoLog® TEAR rate. No replacement of subject will be performed if subject discontinued prematurely from the study. An attrition rate is not considered; for the analysis an imputation of missing values will be done and no patient will be excluded from the primary analysis.

Table 5: Margins and 95% CIs with different reference TEAR event rates in 500 subjects

Event Rate for Reference Product	Estimated 95% CI for the Event Rate (n=250)	Margin	Type I error 2 one-sided alpha	Power	Total N
5%	(2%,8%)	5.7%	0.05	80%	500
10%	(6%,14%)	7.9%	0.05	80%	500
15%	(11%,19%)	9.3%	0.05	80%	500
20%	(15%,25%)	10.5%	0.05	80%	500
25%	(20%,30%)	11.3%	0.05	80%	500
30%	(24%,36%)	12.0%	0.05	80%	500
35%	(29%,41%)	12.5%	0.05	80%	500
40%	(34%,46%)	12.8%	0.05	80%	500
45%	(39%,51%)	13.0%	0.05	80%	500
50%	(44%,56%)	13.1%	0.05	80%	500
55%	(49%,61%)	13.0%	0.05	80%	500
60%	(54%,66%)	12.8%	0.05	80%	500

7.2 Primary Endpoints

7.2.1 Definition of Primary Endpoints

The TEAR rate during 24-week treatment period is the primary endpoint for this study. TEAR criteria is defined as either one of the following:

1) Subjects who are ADA negative at baseline and become positive at any timepoint post baseline.

2) Subjects who are ADA positive at baseline and demonstrate 4-fold increase in titer values at any timepoint post baseline visit.

Whether a subject sample is ADA positive or negative will be determined using screening and confirmatory assays in a tiered approach. Titer values will be further evaluated if a subject sample is confirmed ADA positive. If the subject is ADA positive at baseline, then the titer values of post baseline samples will be further evaluated to determine if there is a 4-fold increase versus baseline, indicating that the post-baseline sample(s) are treatment boosted ADA positives (see Section 6.5.2.4. in protocol for detailed immunogenicity assessment information).

Although differences in TEAR rate is the primary endpoint for the study from a statistical perspective, given that immunogenicity is not a standard endpoint in clinical trials, this difference, even if significant, will not be assessed in isolation but will be part of totality of evidence including changes in HbA1c, FPG, insulin dose, neutralizing antibodies and injection site reactions to ensure that changes in TEAR rate, if any, are clinically correlated and meaningful.

7.2.2 Statistical Methodology for Primary Endpoints

The 90% confidence interval of treatment difference (MYL-1601D minus NovoLog®) in TEAR rate will be established using Wald confidence limit method. MYL-1601D TEAR rate is equivalent to that of NovoLog® during 24-week treatment period if 90% confidence interval of treatment difference in TEAR rate is within pre-specified margin defined in Table 5. The pre-specified equivalent margin is dependent on the final rate of NovoLog® TEAR rate.

To minimize any bias due to missing data, multiple imputation will be used to fill in missing values for TEAR criteria (binary response and continuous titer values) prior to deriving the TEAR and subsequently estimating the treatment difference and 90% confidence interval.

The method of imputation for a subject will be dependent on the individual ADA result at baseline. For subjects with baseline ADA negative, post baseline binary response (positive or negative) will be imputed using logistic regression multiple imputation assuming missing not at random. For subjects with baseline positive, missing titer values (continuous values) will be imputed with same treatment group non-missing subjects using pattern mixture model with the complete-case missing values (CCMV) method (Little 1993).

In the case where there are sufficient number of retrieved dropouts, that is, if there are 6 retrieved dropout subjects in each treatment group, the missing values in that treatment group will be imputed by modelling the retrieved subgroup data. Retrieved dropout subjects are the subjects who discontinued assigned study treatment but still remain on the study and had their

efficacy and safety measurements captured at the planned visits. If less than 6 retrieved dropout subjects in each treatment group, all non-missing subjects within same treatment group will be used to impute missing data by multiple imputation.

If baseline value is missing, the missing baseline value will be imputed with single imputation based on binomial distribution using probability of no missing baseline values from same treatment group.

After imputation, the TEAR criteria will then be applied to each imputed dataset to obtain if a subject is TEAR positive or negative, and the treatment difference and 90% confidence interval will be estimated using Wald confidence limit method. The result will be combined over all imputations by SAS PROC MIANALYZE.

The primary analysis will be based on the ITT analysis set. In addition, all post-discontinuation and rescue data should be included in the analysis. Further analysis details analysis steps and example SAS codes will be provided in the SAP.

7.2.3 Primary Analysis for Primary Endpoints

Equivalence of TEAR rate will be established if 90% confidence interval of treatment difference (MYL-1601D minus NovoLog®) is within ± margin indicated in Table 5. The pre-specified equivalence margin is based on the final NovoLog® TEAR rate. The primary analysis will be performed on the intent to treat (ITT) analysis set.

7.2.4 Secondary/Sensitivity Analyses for Primary Endpoints

- Same analysis model as the primary analysis, but without imputing missing values. This will be analyzed based on PP and ITT analysis set.
- In a derived TEAR dataset, for subjects in MYL-1601D treatment group with missing antibody values, TEAR responder will be replaced regardless if subject is TEAR responder or non-responder. The TEAR rate difference between two treatments and 90% confidence interval will be then estimated using Wald confidence limit method. This will be analyzed based on ITT.
- Tipping-point analysis using method proposed by Liublinska and Rubin (2014) will be performed. A graphic display (heating map) is used to indicate the tipping point analysis results with missing values as TEAR positive. The treatment differences are presented as values in the heat map. The graph will be displayed to show the sensitivity ranging from missing favour testing treatment to missing favour reference treatment.

  For tipping-point analysis, number of subjects with missing data are either 1) subjects who miss completely post-baseline ADA data or 2) subjects who miss partially ADA data that cannot be determined if subject is TEAR positive or negative 3) subjects who miss at baseline. If a subject with partially ADA missing data already meet the TEAR criteria, the subject is not considered as subject with missing data.
- TEAR rate for each treatment and difference between treatments for missing data during treatment period will be summarized for all sensitivity analyses.
- In addition, incidence of TEAR rate at each scheduled visits: visitwise TEAR (vTEAR) will be summarized at each scheduled visit by using similar TEAR

definition: ADA negative at baseline become positive at specific visit (Treatment Induced TEAR), and ADA positive at baseline and become 4-fold increase in titer at specific visit (Treatment Boosted TEAR).

7.2.5 Missing Data

The only imputed data will be performed in the primary and sensitivity analyses as described above for TEAR rate associated with ADA and other secondary variables if deemed necessary. The detailed missing data imputation for other secondary variables will be included in SAP.

7.2.6 Sub-Group Analyses

Subgroup analyses of important factors, including but not limited to factors such as age group, gender, race, and ethnicity are planned for the key outcomes of TEAR rate. Wald confidence limit method for TEAR rate will be used for 90% confidence interval. 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. A mixed model repeated measures (MMRM)-effects model will be performed for continuous variables without imputing missing values. 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 value as covariates. 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 HbA1c from baseline.
- Change in fasting plasma glucose from baseline.
- Change in prandial, basal insulin and total daily insulin dose per unit body weight (U/kg) from baseline.
- Change in 7-point SMBG profile from baseline.

All above analyses will be performed on ITT set.

A sensitivity analysis for HbA1c will be performed using multiple imputation to impute missing values with non-missing subjects within same treatment group using pattern mixture model with the complete-case missing values (CCMV) method (Little 1993). After imputation, treatment difference, 95% CI, and p-values will be generated using same MMRM model as above.

The following safety measures (both actual and change values) will be summarized at baseline and scheduled visit. Similar MMRM model as efficacy analysis will be conducted for hypoglycemia rate. For antibody continuous variables, 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 and baseline value as covariates. 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 following analyses will also be performed and will form part of the totality of evidence to compare clinical efficacy and safety of two treatment groups:

- Incidence of ADA response and positive cross-reactive ADA; and incidence of positive NAbs.
- Analysis of potential impact of TEAR status on efficacy and safety parameters such as HbA1c, glucose control FPG, insulin dose, hypoglycemic rate, incidence of any injection site allergic reactions and hypersensitivity.
- Change in hypoglycemia rate (30 day adjusted) from baseline and incidence of hypoglycemic events at scheduled visits
- Incidence of TEAEs and SAEs
- Incidence of local allergic reactions, systemic allergic reactions and other adverse events
  Incidence of device-related safety assessment

To explore the potential ADA impact on subject's glucose control, the following analyses will be performed:

- The incidence of subjects with meeting all three following criteria will be summarized descriptively (for categorical measures) by treatment, by visit, and overall:
  1) Meet the vTEAR criteria
  2) Increases in HbA1c of over 0.2% from baseline
  3) Increase in total dose from baseline
- Scatter plots of maximum TEAR values with HbA1c, FPG and total daily insulin dose by treatment.

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 device-related patient's complaints, incidence will be listed and summarized for each treatment.

All the above analyses will be performed on the safety set.

In addition, graphical visualization of relationship between adverse events and treatment duration will be provided.

The details of all safety analysis will be provided in the SAP.

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 24 and do not have protocol violations that impact the primary outcome (as detailed in the statistical analysis plan).

Subjects who take other fast acting insulin other than assigned study medication such as rescue medication will be excluded from PP analysis set. The subjects excluded from the PP analysis set 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.

Run-in analysis set includes all subjects who enrolled into run-in period.

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 summarized and listed on run-in analysis set.

Treatment emergent adverse events and concomitant medications will be summarized and listed. All AEs that occur after the first dose of study treatment medication after randomization through follow-up visit or 14 days after last dose [for subjects that do not have a follow-up visit] 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.

7.5.1 Vital Signs

Change from baseline of vital sign measurements will be analyzed using MMRM with model terms of Investigator, 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 by treatment groups.

7.5.2 ECG Analyses

The percentage of subjects in categories such as normal, abnormal/non-clinically significant and abnormal/clinically significant will be summarized by treatment groups

7.5.3 Laboratory Data

Change from baseline of laboratory measurements will be analyzed using MMRM with model terms of Investigator, 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 normal, abnormal/non-clinically significant and abnormal/clinically significant will be summarized by treatment group.

The percentage of subjects in categories such as potentially clinically significant will be summarized by treatment groups. The potentially clinically significant criteria will be listed in SAP.

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.
    - Signs, symptoms, or the clinical sequelae of a suspected drug-drug or drug-food interaction.
    - Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent; this should be reported regardless of sequelae.

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-1601D 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-1601D is the IB. For NovoLog® and Lantus® 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, and following 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. The diary data is considered as source data. 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 5 or the latest version. 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 6: 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 (not applicable if using CTCAE 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 7.

Table 7: 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 before intake of study treatment. 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 assess 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 8: 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, if the relationship to the study treatment(s) is considered to be unlikely or not related/unrelated, an alternative suspected etiology should 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 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 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 or 14 days after last dose of study medication. 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 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 medical 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 (preferred) or fax 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 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. If available, a death certificate should be included.

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 of awareness by email (preferred) or fax to:

Mylan Product Safety & Risk Management

PV MAIL HUB FOR IMMEDIATE SAFETY REPORTS:

pvclinical@mylan.com

In the event 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. An email acknowledgement that the fax was received will be sent within 24 business hours of receipt of the fax.

The Investigator or the site staff can reach out to study CRO through a 24-hour helpline for any emergency medical related questions at +1.919.674.5468 or +1.888.426.8801 (toll free).

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

Any pregnancy occurring after randomization to study drug will be followed up and reported to the Sponsor as per Section 9.4.1 The Investigator should report the pregnancy within 24 hours of awareness 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 any stage of the study will be discontinued immediately from the study. Early termination 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 an elective procedure and not an AE, nevertheless, Mylan requests that the outcome (e.g., elective termination) be reported within 24 hours of awareness and sent as a follow-up report on the Delivery and Infant Follow-up Form.

If the subject consents to be followed, the Investigator will be required to follow the pregnancy at 3 monthly intervals until delivery or termination, informing the Sponsor about its outcome.

If the study center becomes aware of a pregnancy in a female partner of a male subject, study personnel should contact their clinical research associate to obtain a partner pregnancy ICF. Consent of the pregnant partner must be obtained before any details of the pregnancy can be shared with Mylan or its designated representative. If the pregnant partner provides consent to have the pregnancy followed, the study center should collect the information specified on the pregnancy report form and forward the completed form to Mylan PSRM in quarterly intervals until the pregnancy outcome has been obtained.

Non-exposed partner pregnancies (conception occurring prior to receipt of first dose of the study treatment and those occurring after the last dose of study treatment) do not need to be reported or followed. A male that has a partner that becomes pregnant during the study will not be discontinued from study treatment.

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 early termination from the study, additional concomitant drug treatment, or other therapy; and/or
- The test result is considered 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.

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