TITLE PAGE: PHASE 3 CLINICAL TRIAL

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

Compound Number:	NA
Compound Name (if applicable):	Insulin Glargine
US IND Number (if applicable):	IND 105279
European Clinical Trial Database (EudraCT) Number (if applicable):	2015-004353-40
Protocol Number:	MYL-1501D-3003
Phase:	3
Sponsor:	Mylan GmbH Thurgauerstrasse 40, 8050 Zürich Switzerland
Status:	Final
Version:	2.0
Date	06-May-2016

APPROVAL SIGNATURES

PROTOCOL #	VERSION	PROTOCOL TITLE	EFFECTIVE DATE
MYL-1501D-3003	2.0	An Open-label, Randomized, Multi-center, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus® in Type 1 Diabetes Mellitus Patients-An Extension Study.	06-May-2016

I, the undersigned, have read this protocol and confirm that to the best of my knowledge the protocol accurately describes the planned conduct of the study, meets all necessary requirements of appropriate Standard Operating Procedures (SOPs) and has been reviewed and endorsed by the appropriate persons for Clinical Operations, Clinical Development and Statistics.

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Date 9-May-2016

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Date 09-May-2016

Document History

Document	Version Date	Summary of Changes
MYL-1501D-3003 Clinical Trial Protocol	1.0, 09-Oct-2015	N/A

MYL-1501D-3003
Clinical Trial Protocol
Amendment
	2.0, 06-May-2016	• Approval Signatures page:
		Version and effective date are changed.
		Sponsor's personnel and designations changed (Approval Signatures).
		• In the section Contact Details For Reporting Serious Adverse Events, the sentence "Any SAE occurring in a subject from consent until 28 days after the last dose of the study drug must be reported" has been replaced with "Any SAE occurring in a subject from consent until his/her last study visit/phone visit (scheduled or unscheduled) must be reported".
		• The Synopsis and section 2.1, the wording of the Primary and the Secondary objective of Immunogenicity, were modified for clarity.
		• The Synopsis and sections 3.1 and 9.1, number of patients (from estimated 110 patient to estimated 138 patients) and sites (from estimated 80 to estimated 70) were modified.
		• The Synopsis, Schedule of Activities, Study Flowchart [Figure 1], Sections 1.1, 3, 3.1, 6.1, 6.2, table 3 were modified to include additional treatment period, weeks 24-36.
		• The following changes made to the Schedule of Activities:
		  • Clarification made regarding certain data captured in MYL-GAI-3001 that will be reused in MYL-1501D-3003 (Footnotes #8 and #11).
		  • Clarification on informed consent made (Footnote #3).

		• Clarification made regarding ongoing adverse events from MYL-GAI-3001 (Footnote #8). • Clarification made that allergic reactions, AEs and SAEs will be captured during the follow up period (Footnote #12). • Sections 1.1, Background and Rationale. Explanation and rationale for the study design change is provided. • Section 5.4 - Clarification made regarding opened and expired study medication. • Synopsis and Section 6.2. To minimize missing data, clarification added that patients who have been prematurely withdrawn from treatment will be followed up until the 40 week follow-up call in case consent is provided. • Schedule of Activities, Section 7.3, Table 4. Blood collection for immunogenicity analysis added at 4, 26, 28, 32 and 36 weeks. • Sections 7.3 and 7.4.10. Details of central laboratories for immunogenicity and safety analyses modified. • Sections 7.3.1 and 7.3.2. Methodology for immunogenicity assessments were modified. • Sections 7.4.1 and 7.4.2. Clarifications made regarding medical history and prior and concomitant medications. • Section 7.5.4. Clarification made regarding dilated ophthalmoscopy/ retinal photography testing. • Section 8.3. Clarification made regarding the collection period for AEs and SAEs; text on reporting for withdrawn patients removed, as this is covered in. • Section 9. Modifications made throughout the data analysis/statistical methods section. • Section 9.2.1. Text regarding primary

		endpoint modified to accommodate addition of treatment period. • Section 9.2.2. The primary analysis population changed from ITT to mITT; descriptive text on analysis populations added. • Section 9.7. The primary efficacy analysis changed from non-inferiority to equivalence. • Investigator Agreement Page added to body of protocol (previously appended separately). • Minor editorial and formatting corrections made throughout the protocol.

CONTACT DETAILS FOR REPORTING SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is any event which is fatal or life-threatening, requires or prolongs hospitalization, is significantly or permanently disabling or incapacitating, constitutes a congenital anomaly or birth defect, is medically significant, or requires medical or surgical intervention to prevent one of these outcomes (please see section 8.2.4 for a detailed definition).

Any SAE occurring in a subject from consent until his/her last study visit/phone-visit (scheduled or unscheduled) must be reported.

The Investigator will ensure that the SAE reporting form is completed and emailed/faxed by the Investigator to the Pharmacovigilance department, Mylan, within 24 hours of learning of the occurrence of any SAE, even if the SAE does not appear to be drug-related. The original SAE reporting form, together with the email/fax confirmation sheet, must be kept with the case report forms at the study site. More details are provided in the protocol.

Pharmacovigilance Department

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	American Diabetes Association
ADR	adverse drug reaction
AE(s)	adverse event(s)
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
DCCT	Diabetes Control and Complications Trial
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration (United States)
FPG	fasting plasma glucose
GCP	Good Clinical Practice
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HCP	host cell protein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's brochure

Abbreviation	Definition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	Intention to treat
IU	International Unit
IVRS	interactive voice response system
IWRS	interactive web response system
JNC	Joint National Committee
LDL	low density lipoprotein
LOCF	last observation carried forward
MDP	manic depressive psychosis
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NPH	neutral protamine Hagedorn
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	Per protocol
SAE(s)	serious adverse event(s)
SD	standard deviation
SMBG	self-monitored blood glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title	An Open-label, Randomized, Multi-center, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus® in Type 1 Diabetes Mellitus Patients: An Extension Study
Objectives	To compare the following variables when Mylan's insulin glargine and Lantus® are interchanged: Primary objective • Demonstrate the equivalence of changes in HbA1C between two treatment sequence groups Secondary objective • Change in basal insulin dose per unit body weight (U/Kg/day) • Immunogenicity: incidence and change from baseline in the relative levels of ADA, incidence and change from baseline in the relative levels of anti-HCP antibodies. • Rate of hypoglycemic events per 30 days and occurrence of hypoglycemia • Occurrence of local reactions, systemic reactions and other adverse events • Change in fasting plasma glucose • Change in 8-point SMBG profile • Device-related safety assessments
Proposed Number of Sites	From approximately 70 selected sites, approximately 69 patients will be included in each arm, with a target of approximately 138 randomized patients in both arms together.
Study Population	Patients with an established diagnosis of T1DM per ADA 2014 criteria who were randomized to the Lantus® treatment arm of the MYL-GAI-3001 study, and who have completed the 52-week treatment period on Lantus® will be eligible to be screened for the MYL-1501D-3003 study.
Duration of Patient Participation	The maximum possible duration of patient participation in the extension study is approximately 40 weeks, which includes: 1. Randomized comparative treatment period 1: 12 weeks. 2. Randomized comparative treatment period 2: 12 weeks. 3. Randomized comparative treatment period 3: 12 weeks. 4. Follow-up period: 4 weeks.
Study Design	This multi-center, open-label, randomized clinical extension study in patients with T1DM will assess interchangeability of Mylan's insulin glargine and Lantus® with respect to safety and efficacy. Patients with an established diagnosis of T1DM per ADA 2014 criteria who were randomized to the Lantus® treatment arm of the MYL-GAI-3001 study, and who have completed the 52-week treatment period on Lantus® will be eligible to be screened for the MYL-1501D-3003 study. There will be 2 treatment arms (with 3 sequences) in the extension study. Patients randomized to Lantus® during MYL-GAI-3001 will be randomized to either Lantus® or Mylan's insulin glargine for 12 weeks. After this first 12 weeks of treatment, those on Mylan's insulin glargine will be switched to Lantus® while those on Lantus® will continue on Lantus® for another 12 weeks to complete the second treatment period. After 24 weeks of treatment, those patients who were randomized to Mylan's insulin glargine and had a switch to Lantus® will undergo an additional switch to Mylan's insulin glargine for an additional 12 weeks to complete the third treatment period. Those patients who are on Lantus® since the start of the study and did not have any switch, will continue on Lantus® for another 12 weeks to complete the third

	treatment period. After 36 weeks of treatment, patients will go back to the approved medications (as prescribed) and will be followed up for safety for another 4 weeks (Mylan will not provide any medications from 36 weeks of treatment onwards). The 36 to 40 week safety data will also be captured. During the 36-weeks treatment period, the titration (if needed) of both Mylan's insulin glargine and Lantus® should be kept to a minimum, unless there are safety concerns. The week 52 visit for MYL-GAI-3001 will also serve as the week 0 visit for the extension study.
Number of Patients	From approximately 70 selected sites, approximately 69 patients will be included in each arm, with a target of approximately 138 randomized patients in both arms together.
Inclusion Criteria	Patients must meet all of the following inclusion criteria to be eligible for enrollment into the extension study: 1. Patients who have completed the 52-week treatment period (irrespective of their age at the completion of MYL-GAI-3001) of MYL-GAI-300 and were assigned to Lantus® in MYL-GAI-3001. 2. Patients or their legal representatives must give written and signed informed consent before starting any protocol-specific procedures. 3. The patient is able and willing to comply with the requirements of the extension study protocol including the 8-point SMBG, completion of the patient diary records as per the instructions and following a recommended diet and exercise plan for the entire duration of the extension study. 4. Female patients complying with the following: o Female patients of childbearing potential must be using oral contraception or two other acceptable methods of contraception (e.g., intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.) from the time of randomization throughout the entire study. o Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. o Postmenopausal females must have had no menstrual bleeding for at least 1 year prior to inclusion to MYL-1501D-3003. o Female patients who report surgical sterilization must have had the procedure at least 6 months prior to inclusion to MYL-1501D-3003. o All female patients of childbearing potential, must have negative pregnancy test results at baseline (week 0) and at each clinic visit as per the SCHEDULE OF ACTIVITIES. o If female patients have male partners who have undergone vasectomy, the vasectomy must have occurred more than 6 months prior to inclusion in MYL-1501D-3003.
Exclusion Criteria	Patients meeting any of the following criteria will not be included in the extension study: 1) History or presence of a medical condition or disease that in the Investigator's opinion would place the patient at an unacceptable risk from trial participation. 2) History of clinically significant (i.e., significant enough to alter the insulin dose requirement, as per the Investigator) acute bacterial, viral or fungal systemic infections in the 4 weeks prior to inclusion / randomization (recorded while collecting patient history) in the MYL-1501D-3003 extension study. 3) Patients scheduled to receive another investigational drug during the extension study period. 4) Any major elective surgery requiring hospitalization planned during the extension study period. 5) Moderate insulin resistance, defined as requiring insulin (Basal + Prandial) of ≥1.5 U/kg/day (Lantus® in U/kg/day or Mylan's insulin glargine in IU/kg/day).
Withdrawal Criteria	If, for any reason, a patient discontinues the trial prematurely, the patient may be followed up

<table>
<tr><td></td><td>upon consent and as described in the following withdrawal criteria:

Following are the withdrawal criteria:

1. Withdrawal of consent.
2. For female patients, diagnosis of pregnancy or stated intention to become pregnant. Effort should be made so that the pregnant women still report to the site and are followed until delivery or termination.
3. Repeated protocol non-compliance.
4. At the investigator's discretion, (following discussion with the sponsor medical monitor), for safety issues such as severe hypoglycemia or hypoglycemic unawareness. The site should follow-up these patients as per the SCHEDULE OF ACTIVITIES until the 40 week follow-up call.
5. At the investigator's discretion, (following discussion with the sponsor medical monitor), in certain situations such as significant intercurrent illness, hospitalization for surgery, or an SAE. The site should follow-up these patients as per the SCHEDULE OF ACTIVITIES until the 40 week follow-up call.</td></tr>
<tr><td>Study Treatments</td><td>Investigational Products
• Mylan's insulin glargine (test product) 100 IU/mL
• Lantus® from Sanofi-Aventis sourced from the US (US listed drug) 100 U/mL
Both investigational products will be provided in a pre-filled disposable pen with a 3 mL cartridge.
Mealtime insulin
• Humalog® (insulin lispro injection, 100 U/mL), manufactured by Eli Lilly (administered in Humalog Kwikpen® disposable pens).
All patients will continue on insulin lispro for the complete trial. The Investigator will inform the patients of the doses to be used and the titration scheme to be followed (if needed during the study). During the trial period dose titration (if needed) will be kept to a minimum.</td></tr>
<tr><td>Concomitant Medications and Therapy</td><td>Other than study drugs, insulin, insulin analogs and other anti-diabetes medications as well as glucocorticoid therapy (oral, intravenous, inhaled or other routes that produce systemic effects) should not be taken during the study (prohibited medications).
A list of restricted medications that may interfere with the effect of insulin is given in the below table. No drugs listed in this table should be started during the treatment period.
All treatments being taken by the patients following signing the ICF in addition to the trial treatment (investigational products and mealtime insulin) during the trial are regarded as concomitant medications and must be documented in the CRF. Mylan's insulin glargine, Lantus® and insulin lispro will not be considered as concomitant medications.

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

SCHEDULE OF ACTIVITIES

	Visits													
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13[1] (EOT)	V14[2] (FU)
Extension Study Week	0	2	4	8	12	14	16	20	24	26	28	32	36	40
Extension Study Day	0	14±3	28±3	56±3	84±3	98±7	112±7	140±7	168±7	182±7	196±7	224±7	252±7	280±7
Informed Consent[3]	x													
Inclusion/Exclusion Criteria Review	x													
Previous and current insulin usage history	√													
Dilated Ophthalmoscopy / Retinal photography testing[4]	x	x	x											
Standard-of-care specifics[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	
Age, Gender, Race	x													
Body Weight, Height and BMI[11]	√												x	
Pregnancy Test[6]	√	x	x	x	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	
Vitals signs measurement (sitting)	√	x	x	x	x	x	x	x	x	x	x	x	x	
Physical examination	√	x			x	x			x	x			x	
12-lead ECG (supine)	√				x	x			x	x			x	
Fresh Randomization with capture of old randomization number[7]	x													
Record AEs and SAEs, local and systemic allergic reactions and hypoglycemic events[8]	x	x	x	x	x	x	x	x	x	x	x	x	x	x[12]
Record device safety information (disposable needle or pen)		x	x	x	x	x	x	x	x	x	x	x	x	
Fasting Plasma Glucose	√			x	x			x	x				x	
HbA1c Assay	√				x				x				x	
HIV, HBsAg, and HCVAb	√													
Sampling for hematology, blood chemistry and urinalysis[9]	√				x				x				x	
Fasting lipid profile	√				x				x				x	
Sampling for immunogenicity	√	x	x	x	x	x	x	x	x	x	x	x	x	
Review 8-point SMBG Profile performed in the week before the visit [10]	√	x	x	x	x	x	x	x	x	x	x	x	x	
Dose review of Mylan's insulin glargine/Lantus® and insulin lispro and instruction	x	x	x	x	x	x	x	x	x	x	x	x		
Dispense Trial Medication and ancillary supplies	x		x	x	x		x	x	x		x	x		

	Visits													
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13[1] (EOT)	V14[2] (FU)
Extension Study Week	**0**	**2**	**4**	**8**	**12**	**14**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**
Extension Study Day	**0**	**14±3**	**28±3**	**56±3**	**84±3**	**98±7**	**112±7**	**140±7**	**168±7**	**182±7**	**196±7**	**224±7**	**252±7**	**280±7**
Drug Accountability and Compliance		x	x	x	x	x	x	x	x	x	x	x	x	
Dispense patient diary	x	x	x	x	x	x	x	x	x	x	x	x		
Review patient diary		x	x	x	x	x	x	x	x	x	x	x	x	

1. At the EOT the Investigator will discuss with the patient the prescription medication that the patient should take after the end of the extension study, and provide dosing instructions. (Mylan will not provide any medications from 36 weeks of treatment onwards)
2. Follow-up visit will be a telephone contact.
3. Informed consent should be signed on the Day "0" prior to initiating any study related activities
4. Dilated Ophthalmoscopy / Retinal photography testing should be performed once within one of the visits during the 28 days of enrolment
5. 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.
6. Urine pregnancy test will be conducted at specified visits. Results of the pregnancy test should be confirmed as negative before dispensing trial drug(s).
7. The MYL-GAI-3001 randomization number should also be captured during the new randomization along with the new randomization numbers.
8. Hypoglycemia that had occurred before MYL-1501D-3003 week 0 visit will be noted in source document and will be used for comparisons. . Ongoing adverse events from MYL-GAI-3001 will be recorded as adverse events.
9. A routine urine dipstick will be performed by the site. A urinalysis by microscopic urinalysis may be performed by the central lab if the dipstick result is abnormal, and if requested by the Investigator.
10. The 8-point SMBG profile measurement needs to be done by the patient at home on any 3 days (of which 2 days should be consecutive) in the week of the visit (i.e. during the 7 days before the day of the visit).
11. Only body weight will be measured at EOT visit. Height at V1 of MYL-GAI-3001 will be used to calculate BMI.
12. Allergic reactions, AEs and SAEs will be captured.

'√' represents information already collected in the MYL-GAI-3001 trial. The same information should be used in this extension study.

'x' represents new information to be collected in the extension study.

AE: adverse event; BMI: body mass index; ECG: electrocardiogram; EOT: end of treatment; HbA1c: glycosylated hemoglobin; HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C virus antibody; HIV: Human Immunodeficiency Virus; SAE: serious adverse event; SMBG: self-monitored blood glucose.

Hematology panel will include hemoglobin, hematocrit, white blood cell count with differentials, red blood cell count with indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration) and platelet count.

Blood chemistry panel will include blood urea / BUN, serum creatinine, creatinine kinase, uric acid, serum bilirubin (total and direct), total protein, serum albumin, ALT, AST, alkaline phosphatase, LDH, lipase, sodium, potassium, calcium, magnesium, chloride, and bicarbonate.

For the urinalysis a routine urine dip will be performed by the site, using supplies provided by the central laboratory. This will include assessment of specific gravity, pH, and semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood. If the investigators want to do detailed urine testing, the site will send a urine sample to the central laboratory for microscopic evaluation. Microscopic examination will include WBC, RBC, casts, cast type, crystals, epithelial cells, renal cells, mucus threads, bacteria, yeast, and Trichomonas)

Physical examination activities will include the following assessments: general appearance, head, ears, eyes, nose and throat (including thyroid), skin, respiratory system, cardiovascular

system, abdomen, lymph nodes, musculoskeletal system, gastrointestinal system (including mouth) and neurological system; and a diabetic foot examination

1. INTRODUCTION

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 primary cause of beta-cell loss is a T-cell mediated autoimmune attack [1]. The principal treatment of patients with T1DM is initiation of insulin and diet control and careful monitoring of blood glucose levels.

Long-acting insulin analogs have proven efficacy and offer good glucose control over 24 hours for a single dose. Insulin glargine is a long-acting insulin analogue allowing once-daily administration to cover basal insulin requirements for over 24 hours. Mylan's insulin glargine is a human insulin analogue of r-DNA origin produced in the host organism *Pichia pastoris*. *P pastoris* is a methylotropic yeast that has been successfully used in the production of proteins.

Extension Study Population: Patients with an established diagnosis of T1DM per ADA 2014 criteria [4] who were randomized to the Lantus® treatment arm of the MYL-GAI-3001 study, and who have completed the 52-week treatment period on Lantus® will be eligible to be screened for the MYL-1501D-3003 study.

1.1 Background and Rationale

Mylan's insulin glargine is being developed globally as a biosimilar to Lantus. In the US, this development is currently following the 505(b)(2) pathway, but will according to the US Food, Drug and Cosmetic (FD&C) Act in the future follow the 351(k) pathway. Hence, criteria for both regulatory pathways will be pursued.[1]

The aim of this extension study is to demonstrate that Mylan's insulin glargine and Lantus® have equivalent safety and efficacy in T1DM patients, when one treatment is substituted with the other. Under the 505(b)(2) pathway this is called "therapeutic equivalence" while under

[1] By March 23, 2020 insulin glargine under section 505 of the FD&C Act shall be deemed to be licensed under section 351 of the Public Health Service (PHS) Act (see section 7002(e)(4) of the BPCI Act) (ref: FDA draft guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf) as a biosimilar

351(k) this is termed "interchangeability". Following the transition from 505(b)(2) to 351(k), the clinical equivalence data will be considered to support the interchangeability of Mylan's insulin glargine and Lantus. Although FDA has not yet issued clear guidelines on interchangeability, interactions with the Agency indicate that in order to show interchangeability between the reference drug and the test drug, the primary endpoint should be assessed for equivalence between two treatment arms; one exposed to continuous use of reference and one exposed to repeated switches, which is defined as at least four (4) periods of adequate durations [three (3) switches or transitions]. Within the 3 switches, the patients will be switched from reference drug to test drug and back again. The Lantus® arm of MYL-GAI-3001 will represent the first of the four periods.

The extension study will be conducted open-label since the 2 formulations have different manufacturers and thus distinct packaging. To avoid bias in the evaluation of the critical endpoints, blinded analysis of immunogenicity and HbA1c data is planned.

Patients who successfully completed 52 weeks in MYL-GAI-3001 will be eligible to participate in the extension study. Patients exposed to different types of insulins may have different immune responses following exposure to trial drug. This confounding effect will be minimized as only patients who have been on Lantus® (besides mealtime insulin lispro) for the last 52 weeks prior to the randomization will be included in the trial.

Patients on Lantus® during MYL-GAI-3001 will be randomized to Mylan's insulin glargine or Lantus® for 12 weeks; following which, those on Mylan's insulin glargine will be switched to Lantus®, and those on Lantus® will continue on Lantus® for another 12 weeks. During the consecutive 12-week comparative treatment periods, diabetes treatment will be either maintained or further controlled (if needed) by titrating the dose of Lantus® or Mylan's insulin glargine, if necessary. After the 24 weeks of treatment, those patients who were randomized to Mylan's insulin glargine and had a switch to Lantus® will undergo an additional switch to Mylan's insulin glargine for an additional 12 weeks to complete the third treatment period. Those patients who are on Lantus® since the start of the study and did not have any switch will continue on Lantus® for another 12 weeks to complete the third treatment period.

All patients will continue on insulin lispro for the entire duration of the study. After completion of the 36 week treatment, patients will go back to the approved medications (as prescribed earlier, prior to their participation in the MYL-GAI-3001 study) on their own and will be followed up for safety for another 4 weeks (Mylan will not provide any medications during the safety follow-up period). The 36 to 40 week safety data will be captured. This 4-week follow-up visit is to confirm that patients are safe on the prescribed medications.

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

1.2 Clinical data on Lantus®

The only reference safety document for Mylan's insulin glargine is the Investigator's Brochure [6]. The only reference safety document for the comparator is the current United States Prescribing Information of Lantus® [7].

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

To compare the following variables when Mylan's insulin glargine and Lantus® are interchanged:

Primary objective

- Demonstrate the equivalence of changes in $HbA1_C$ between two treatment sequence groups

Secondary objective

- Change in basal insulin dose per unit body weight (U/Kg/day)
- Immunogenicity: incidence and change from baseline in the relative levels of ADA, incidence and change from baseline in the relative levels of anti-HCP antibodies.
- Rate of hypoglycemic events per 30 days; and occurrence of hypoglycemia

- Occurrence of local reactions, systemic reactions and other adverse events
- Change in fasting plasma glucose
- Change in 8-point SMBG profile
- Device-related safety assessments

3. STUDY DESIGN

A schematic representation of the extension study is given in Figure 1. This multi-center, open-label, randomized clinical extension study in patients with T1DM will assess interchangeability of Mylan's insulin glargine and Lantus® with respect to the safety and efficacy.

Patients with an established diagnosis of T1DM per ADA 2014 criteria who were randomized to the Lantus® treatment arm of the MYL-GAI-3001 study, and who have completed the 52-week treatment period on Lantus® will be eligible to be screened for the MYL-1501D-3003 extension study. All patients will continue on insulin lispro for the entire duration of the study.

There will be 2 treatment arms (with 3 sequences) in the extension study.

- Patients randomized to Lantus® during MYL-GAI-3001 study will be randomized to either Lantus® or Mylan's insulin glargine for 12 weeks.
- After this first 12 weeks of treatment, those on Mylan's insulin glargine will be switched to Lantus® while those on Lantus® will be continued on Lantus® for another 12 weeks to complete the second treatment period.
- After the 24 weeks of treatment, those patients which were initially randomized to Mylan's insulin glargine and had a switch to Lantus® will have an additional switch to Mylan's insulin glargine for additional 12 weeks to complete the third treatment period. Those on Lantus® since the start of the study, who did not have any switch will continue on Lantus® for another 12 weeks to complete the third treatment period.

After 36 weeks of treatment, patients will go back to the approved medications (as prescribed earlier) and followed up for safety for another 4 weeks. The 36 to 40 week safety data will be captured/documented (Mylan will not provide any medications during the safety follow-up period).

During the 36-week treatment period, the titration (if needed) of both Mylan's insulin glargine and Lantus® should be kept to a minimum and the recommended titration algorithm should be followed, unless there are safety concerns.

The week 52 visit for the MYL-GAI-3001 study will also serve as the week 0 visit for the extension study.

3.1 Study Duration

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

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

Number of Patients:

From approximately 70 selected sites, approximately 69 patients will be included in each arm, with a target of approximately 138 randomized patients in both arms together.

3.2 Allocation to Treatment

Patients on Lantus® will be randomized 1:1 to receive either Mylan's insulin glargine or Lantus® using an IVRS/IWRS. Change of dosing from morning to bedtime or vice versa will not be permitted.

If a patient discontinues, the patient will not be allowed to re-enter the extension study.

3.3 Patient Numbering

The center numbers will remain the same as those assigned by the sponsor/designee in MYL-GAI-3001. New unique randomization numbers will be assigned by the IVRS/IWRS system to the patients enrolled into the MYL-1501D-3003 extension study.

3.4 Blinding

This is an open-label study. To minimize bias, treatment assignments will not be revealed to the central laboratory for the safety (immunogenicity) and efficacy (HbA1c) analyses. A document listing the trial team members who are blinded and unblinded will be maintained.

3.5 Breaking the Blind

The Investigator and the patients will not be blinded to treatment assignments.

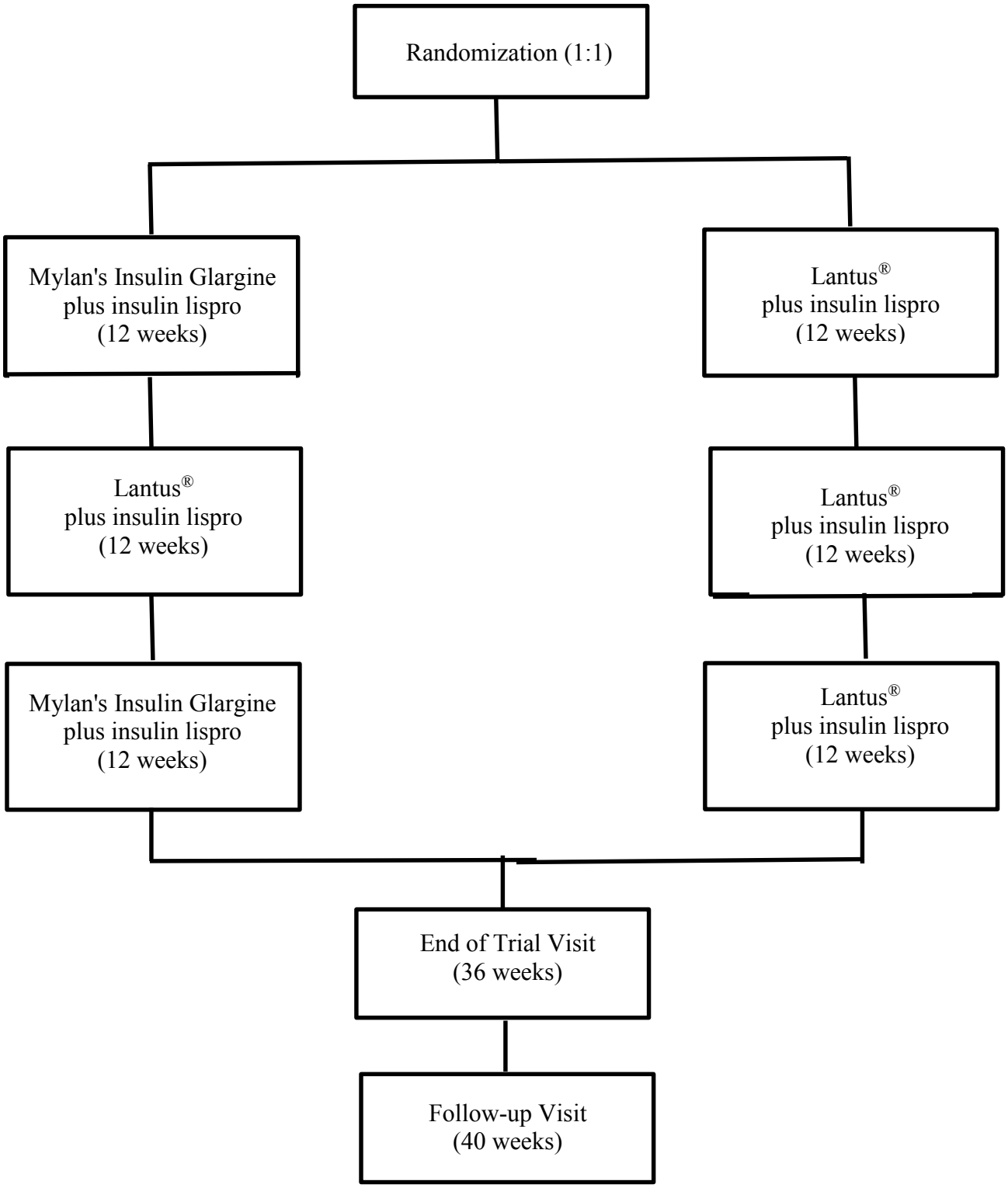

Figure 1: Study Flowchart

4. PATIENT SELECTION

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the extension study:

1. Patients who have completed the 52-week treatment period (irrespective of their age at the completion of MYL-GAI-3001) of MYL-GAI-3001 and were assigned to Lantus® in that study.
2. Patients or their legal representatives must give written and signed informed consent before starting any protocol-specific procedures.
3. The patient is able and willing to comply with the requirements of the extension study protocol including the 8-point SMBG, completion of patient diary records as instructed and following a recommended diet and exercise plan for the entire duration of the extension study.
4. Female patients complying with the following:

    - Female patients of childbearing potential must be using oral contraception or two other acceptable methods of contraception, (e.g., intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.) from the time of randomization throughout the entire study.
    - Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Postmenopausal females must have had no menstrual bleeding for at least 1 year prior to inclusion in MYL-1501D-3003 study.
    - Female patients who report surgical sterilization must have had the procedure at least 6 months prior to inclusion to MYL-1501D-3003 study.
    - All female patients of childbearing potential, must have negative pregnancy test results at baseline (week 0) and at each clinic visit as per the SCHEDULE OF ACTIVITIES.

- If female patients have male partners who have undergone vasectomy, the vasectomy must have occurred more than 6 months prior to inclusion in MYL-1501D-3003 study.

4.2 Exclusion Criteria

Patients meeting any of the following criteria will not be included in the extension study:

1. History or presence of a medical condition or disease that in the Investigator's opinion would place the patient at an unacceptable risk from trial participation.
2. History of clinically significant (i.e., significant enough to alter the insulin dose requirement, as per the Investigator) acute bacterial, viral or fungal systemic infections in the 4 weeks prior to inclusion / randomization (recorded while collecting patient history) into MYL-1501D-3003.
3. Patients scheduled to receive another investigational drug during the extension study period.
4. Any major elective surgery requiring hospitalization planned during the extension study period.
5. Moderate insulin resistance, defined as requiring insulin (basal + prandial) of ≥1.5 U/kg/day (Lantus® in U/kg/day or Mylan's insulin glargine in IU/kg/day).

5. STUDY TREATMENTS AND CONCOMITANT MEDICATION

The investigational products used in this trial are Mylan's insulin glargine and Lantus® (from Sanofi-Aventis). All patients will receive insulin lispro as mealtime medication.

5.1 Study Medication

- Mylan's insulin glargine (test product) 100 IU/mL
- Lantus® 100 U/mL (Sanofi-Aventis), sourced from the US (USLD, reference product)

Both investigational products will be provided by the sponsor in pre-filled disposable pens with a 3 mL cartridge. Mylan's insulin glargine formulation for injection is a sterile, clear solution with a pH of 4. Each mL contains 100 units of insulin glargine (equivalent to 3.64 mg). The excipients of the formulation are identical to those of Lantus® [6]. Please refer to

the Investigator's Brochure [6] for more details on Mylan's insulin glargine, and the United States prescribing information [7] for more details on Lantus®.

At the end of MYL-GAI-3001, an equivalent dose (dose of Lantus® at the end of MYL-GAI-3001) of Mylan's insulin glargine or Lantus® (based on the assigned treatment) will be provided for 12 weeks. For the following 12 weeks, patients on Mylan's insulin glargine will receive the same dose of Lantus®; while patients on Lantus® will continue on the same dose of Lantus®. After 24 weeks of treatment, those patients who were randomized to Mylan's insulin glargine and had a switch to Lantus® will undergo an additional switch to Mylan's insulin glargine for an additional 12 weeks to complete the third treatment period. For those patients who are on Lantus® since the start of the study and did not have any switch will continue on Lantus® for another 12 weeks to complete the third treatment period.

Change in dose should be made only if there is safety concerns as per the Investigator's judgement.

5.2 Mealtime insulin

- Humalog® (insulin lispro injection, 100 U/mL), manufactured by Eli Lilly (administered in Humalog Kwikpen® - disposable pens).

The mealtime insulin will be provided by the sponsor.

HUMALOG 100 units per mL (U-100) is available as 3 mL Humalog KwikPen (prefilled).

Complete information on Humalog® and the Humalog Kwikpen® - disposable pen is available in the Humalog® SmPC and US prescribing information [10,11].

All patients will continue on insulin lispro for the entire duration of the study. The Investigator will inform the patients of the doses to be used and the titration scheme to be followed (if needed during the study). During the trial period dose titration (if needed) will be kept to a minimum.

5.3 Ancillary Supplies

The following ancillary supplies will be provided by the sponsor: glucose monitor, control solution for calibration of the glucometer, glucose monitor strips, alcohol swabs, lancet device, disposable lancets, sharps container, insulated bag to transport insulin, needles, and patient diary.

5.4 Drug Storage

The Investigator must ensure the availability of proper storage conditions and temperature monitoring equipment at the site. A temperature log for trial products stored at the site must be maintained. The Investigator or Investigator's authorized staff will check the storage temperature daily on working days and record the results in the temperature log. If storage conditions deviate from the described storage conditions or the medication is damaged in any way, the monitor must be contacted without delay. The monitor must notify the sponsor of any temperature deviations or damaged products. The sponsor or designee will assess the extent of the temperature deviation or damage and will inform the monitor in writing whether the product may be used or not.

Mylan's insulin glargine 100 IU/mL

Unopened Mylan's insulin glargine disposable pen injector: Mylan's insulin glargine should be stored in a refrigerator (2°C to 8°C). It cannot be used if it has been frozen.

Open (In-Use) Mylan's insulin glargine disposable pen injector: Mylan's insulin glargine can be kept at room temperature (below 25ºC) for up to 28 days once the disposable pen has been put to use. It should not be exposed to heat or direct sunlight. It should never be used after the expiry date printed on the pack.

Lantus® 100 U/mL

Unopened Lantus® disposable insulin pen injector: Lantus® should not be stored in the freezer and should not be allowed to freeze. Lantus® if it has been frozen should not be used. Unopened Lantus® pen injectors should be stored in a refrigerator at 2°C–8°C, and discarded in case expired at the end of the study based on the Sponsor instructions. Unopened Lantus® pen injectors kept at room temperature should be discarded at the end of the study based on the Sponsor instructions.

Open (In-Use) Lantus® disposable insulin device: The opened (in-use) Lantus® pen injector should not be refrigerated but should be kept at room temperature (below 86°F/30°C) away from direct heat and light. The opened (in-use) Lantus® pen injector must be discarded at the end of the study based on the Sponsor instructions .

Please refer to the United States prescribing information for storage conditions for Lantus® [7].

Humalog®

Please refer to the Summary of Product Characteristics [10] (if Europe sourced) or US prescribing information [11] (if US sourced) for Humalog® storage instructions.

Humalog® should not be used after the expiration date. Unopened HUMALOG should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use HUMALOG if it has been frozen. In-use HUMALOG KwikPen should be stored at room temperature, below 86°F (30°C) and must be used within 28 days or be discarded at the end of the study based on the Sponsor instructions, even if they still contain HUMALOG. It should be protected from direct heat and light (Table 1).

Table 1: Humalog Kwikpen Usage Instructions

	Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])	Not In-Use (Unopened) Refrigerated	In-Use (Opened) Room Temperature, (Below 86°F [30°C])
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, do not refrigerate.

5.5 Drug Accountability

The sponsor will supply sufficient quantities of the investigational product to allow completion of this extension trial. Upon receipt of the investigational product supplies at the site, the designated trial staff member should count and verify that the shipment contains all the items noted in the shipment inventory.

The Investigator or designated staff must notify the monitor if there was a temperature deviation during shipment to the site (if information is available) or if the products are in any way damaged (Temp Tale® information should ensure accurate temperature monitoring). The Investigator or designee should temporarily quarantine compromised drug until notified by the monitor of actions to be taken (release for use or permanent quarantine for return and destruction). The monitor must notify the sponsor of any temperature deviations or damaged products. The sponsor or designee will assess the extent of the temperature deviation or damage and will inform the monitor in writing whether the product may be used or not.

The Investigator must keep complete and accurate records for the receipt, storage, dispensing, and return or destruction of investigational products and mealtime insulin.

5.6 Dispensing

It is the responsibility of the Investigator to ensure that investigational products and mealtime insulin are dispensed only to trial patients. The Investigator or designee will dispense the required number of investigational product doses to ensure that the trial patient has sufficient supplies until the next dispensing visit.

Patients will be requested to return all used and unused medications to the site at each visit. The usability of the returned medications will be assessed. Returned medications may be again dispensed to the same patient, provided it was stored as per specification and will not cross the expiry date before the next visit.

The site will store the returned medication until the monitor has performed accountability and informs the site of the processes for destruction or return of the medication.

5.7 Administration

Insulin glargine should be administered as a subcutaneous injection. It should be taken at approximately the same time every day. The preferred site is in the abdomen. The other possible sites of administration are the upper arm and thigh (upper leg). The injection sites should be rotated to reduce risk of lipodystrophy. Refer to the Investigator's Brochure [6] and US prescribing information [7]. Insulin lispro will be administered as per the Investigator's advice and as per the prescribing information [10,11].

The dosage of insulin will be adjusted based on SMBG profile, performed by the patients at home, so that patients attain the following glycemic targets (ADA 2014 criteria) [4]:

- Fasting pre-prandial SMBG between 70 to 130 mg/dL (3.9-7.2 mmol/L)

If the measured SMBG is <70 mg/dL (3.9 mmol/L) or if the patient has symptoms suggestive of hypoglycemia, he/she can call the Investigator or designee, if required. The insulin dose will be altered by the Investigator or designee, if required, based on the values. Any increase in total insulin dose per day of >6 units during any titration step should be performed with caution.

5.8 Return of Study Drug

After the completion of the extension study, the monitor will perform the final drug accountability check and inform the site of the return/destruction procedures for the unused and partly used medication.

5.9 Treatment Compliance

All reasonable and appropriate methods will be used to ensure compliance to the protocol for administration of trial medication.

5.10 Concomitant Medication

Other than study drugs, insulin, insulin analogs and other anti-diabetes medications as well as glucocorticoid therapy (oral, intravenous, inhaled or other routes that produce systemic effects) should not be taken during the study (prohibited medications). A list of restricted

medications that may interfere with insulin is given in Table 2. No drugs listed in this table should be started during the treatment period.

Table 2: Medications That Are Likely to Interfere with Diabetes Control

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

All treatments being taken by the patients following signing the ICF in addition to the trial treatment (investigational products and mealtime insulin) during the trial are regarded as concomitant medications and must be documented in the CRF. Mylan's insulin glargine, Lantus® and insulin lispro will not be considered as concomitant medications.

6. STUDY PROCEDURES

This trial includes randomized comparative treatment period-1, randomized comparative treatment period-2, randomized comparative treatment period-3 and a follow-up period. Specific activities involved in each period are described in the SCHEDULE OF ACTIVITIES.

Throughout the trial, every reasonable effort should be made to follow the timing of assessments and procedures for each patient. Deviations from the schedule should be avoided. The allowed time window for each visit is shown in the SCHEDULE OF ACTIVITIES.

6.1 Visit Schedules and SMBG Profiles

Table 3 shows the SMBG profiling requirements at each visit.

Table 3: SMBG Profile Requirements by Visit

	Weeks 0 to 36	Week 40 (FU)
Mandatory clinic visit with 3 day 8-point SMBG in the week preceding the visit	Week 0 to week 36 visits	-
Telephone visit	As advised by the Investigator	SMBG will be performed for FU visit, as suggested by the Investigator at Week 36 visit (EOT)*

*Additional visits or profiles to be performed as advised by the Investigator
EOT: end of treatment; FU: follow-up visit: SMBG: self-monitored blood glucose.

6.2 Patient Withdrawal

If, for any reason, a patient discontinues the trial prematurely, the patient may be followed up upon consent and as described in the following withdrawal criteria:

Following are the withdrawal criteria:

1. Withdrawal of consent.
2. For female patients, diagnosis of pregnancy or stated intention to become pregnant. Effort should be made so that the pregnant women still report to the site and are followed until delivery or termination.
3. Repeated protocol non-compliance.
4. At the investigator's discretion (following discussion with the sponsor medical monitor), for safety issues such as severe hypoglycemia or hypoglycemic unawareness. The site should follow-up these patients as per the SCHEDULE OF ACTIVITIES until the 40 week follow-up call.
5. At the investigator's discretion, (following discussion with the sponsor medical monitor), in certain situations such as significant intercurrent illness, hospitalization for surgery, or an SAE. The site should follow-up these patients as per the SCHEDULE OF ACTIVITIES until the 40 week follow-up call.

Investigators must attempt to contact patients who fail to attend scheduled visits (by telephone or other means), to exclude the possibility of an AE being the cause of withdrawal. Should an AE be the cause for withdrawal, the AE must be documented, reported, and followed-up as described in Section 8. If withdrawal was not due to an AE the

Investigator should inquire about the reason for withdrawal. If applicable, request all withdrawn patients to bring back all unused investigational product(s) and return them at the final visit. The attempts to contact patients who fail to attend scheduled visits should be documented in the patient files as should the reasons for withdrawal.

No further evaluations should be performed, and no additional data should be collected if the patient withdraws from the trial and also withdraws consent for disclosure of future information. Data collected before patient withdrawal of consent will be retained and continue to be used, or destroyed if required per local regulation and rules.

7. STUDY ASSESSMENTS AND METHODS

7.1 Handling of Blood Samples

Laboratory analysis will be conducted at central laboratories identified by the sponsor. The laboratory will provide specific sample kits to the Investigator site prior to the visit of patients. Instructions for collecting, handling, storing and shipping samples will be provided in the laboratory manuals.

7.2 Efficacy Assessments

7.2.1. HbA1c

HbA1c assessments will be performed as shown in the SCHEDULE OF ACTIVITIES. The measurement will be performed by the central laboratory for safety and efficacy samples.

7.2.2. Fasting Plasma Glucose (FPG)

FPG assessments will be performed as shown in the SCHEDULE OF ACTIVITIES. The measurement will be performed by the central laboratory for safety and efficacy samples.

7.2.3. Body Weight and BMI

Weight will be recorded by the site as specified in the SCHEDULE OF ACTIVITIES**.** The Investigator will calculate the BMI (using the formula BMI=weight in kg/ height in m^2; for BMI calculation, the previous recorded weight will be used until new weight recording).

7.2.4. 8-point SMBG profiles

8-point SMBG profile measurements will be performed by the patient at home and recorded in the patient diary, as specified in the SCHEDULE OF ACTIVITIES. One 8-point SMBG profile set includes measurements of SMBG values on 3 days, performed in the week preceding the next visit (of the three days, 2 should be consecutive). The time points for the 8-point SMBG are provided in Appendix III. The patient should document the 3 pre-visit measurements in the diary, and will be advised to similarly document any additional estimations.

On days in which SMBG is not mandated by protocol, patients will be advised to self-monitor their blood glucose 4 times a day.

7.2.5. Daily Insulin Doses

Patients will be asked to document the dose of Mylan's insulin glargine/Lantus® and insulin lispro taken on the days when they perform 8-point SMBG profiles (from week 0 to week 24). Doses must be recorded in the patient diary. This data will be transcribed to the eCRF after the patient diary is collected, by the Investigator or designee. The patient should document the 3 pre-visit doses in the diary; and will be advised to document any additional doses.

7.3 Immunogenicity Assessments

Blood samples for the assessment of immunogenicity will be collected as specified in the SCHEDULE OF ACTIVITIES and in the table below (Table 4).

Table 4: Blood Volume Needed for Immunogenicity Analysis

Assessments	Randomization[3]	2 weeks	4 weeks	8 weeks	12 weeks	14 weeks	16 weeks	20 weeks	24 weeks	26 weeks	28 weeks	32 weeks	36 weeks
	Volume Collected (mL)												
Anti-drug antibody (ADA)[1]	15	10	10	10	10	10	10	10	10	10	10	10	10
Neutralizing Antibody (NAb)[1]	5	5	5	5	5	5	5	5	5	5	5	5	5
Anti-HCP Antibody[1]	5	5	5	5	5	5	5	5	5	5	5	5	5
Drug	6	6	6	6	6	6	6	6	6	6	6	6	6

Assessments	Randomization[3]	2 weeks	4 weeks	8 weeks	12 weeks	14 weeks	16 weeks	20 weeks	24 weeks	26 weeks	28 weeks	32 weeks	36 weeks
	Volume Collected (mL)												
concentration[2]													

[1]Blood samples will be drawn into serum separator tubes (SST).
[2]Blood samples will be drawn into K_2EDTA plasma tubes.
[3]Results of the samples collected as part of MYL-GAI-3001 trial will be used.

The clinical laboratory will provide specific sample kits to the Investigator site prior to the visit of patients. Instructions for collecting, handling, storing and shipping of clinical samples will be provided in the laboratory manuals. Samples and lab results collected at randomization will be considered as baseline.

The central laboratories are:

Samples from Europe will be sent to	Q^2 (Squared) Solutions The Alba Campus, Rosebank Livingston, EH54 7EG UK
Samples from US will be sent to	Q^2 (Squared) Solutions27027 Tourney Road, Suite 2E Valencia, CA 91355 USA

The site must store the immunogenicity and drug concentration samples at -20°C ± 5°C or lower and ship the samples in batches on a monthly basis to the central laboratory where they will be stored at -80 ± 5°C or below. Primary and backup samples should not be sent in the same shipment. Both immunogenicity and drug concentration samples must be shipped frozen on dry ice. Temperature monitoring devices (e.g. Temp Tale®) must be included in all sample shipments.

7.3.1. Anti-Drug Antibody

Two conventional radioimmunoprecipitation assays (RIPA) were employed for the assessment of anti-drug antibodies (ADA). A two assay approach, applied in a blinded fashion, was utilized due to the potential structural differences between drug products arising from the different host cells used in production. The two assays were identical except for the use of a unique tracer: ^{125}I-Lantus, designated for the 'LAN assay', and ^{125}I-MYL IG, designated as the 'MIG assay'. In both assays samples underwent a pre-treatment step that

included acid dissociation to release any anti-insulin antibodies complexed with free drug, followed by charcoal adsorption of the free insulin analog. The treated samples were then incubated with a fixed amount of each tracer under the following conditions:

- Assay buffer only (no inhibitor)
- Assay buffer containing excess unlabeled MYL IG
- Assay buffer containing excess unlabeled Lantus
- Assay buffer containing excess unlabeled Human Insulin

ADA complex formation with the tracers is measured via gamma counting 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 (12, 13), and current regulatory guidance (14), the assay design employed a screening tier (no inhibition), confirmatory tier (competitive inhibition with excess drug), and characterization tier (competitive inhibition with excess human insulin) that were assessed simultaneously. Since inhibition with excess drug and human insulin were included within the assessment of each sample, the total anti-drug antibody and insulin cross reactivity results were reported in terms of percent specific binding (%SB), which is the difference between the %B/T for the uninhibited and the inhibited samples for each assay. Analogous to titer values, the %SB is the relative amount of antibody present in the samples. Cut-points for these assessments were determined based on %SB during assay validation and applied during sample analysis for scoring total and cross reactive ADA positive samples:

Assay	Assessment	Assessment Definition
MIG	Total ADA	%B/T (no inhibitor) - %B/T (excess MYL IG)
	Cross-reactive ADA	%B/T (no inhibitor) - %B/T (excess human insulin)
LAN	Total ADA	%B/T (no inhibitor) - %B/T (excess LAN)
	Cross-reactive ADA	%B/T (no inhibitor) - %B/T (excess human insulin)

In addition, drug-specific ADA was assessed by determining the %B/T difference between samples inhibited with excess Lantus and MYL IG in each assay:

Assay	Assessment	Assessment Definition
MIG	Drug specific ADA	%B/T (excess LAN) - %B/T (excess MYL IG)
LAN	Drug specific ADA	%B/T (excess MYL IG) - %B/T (excess LAN)

For this assessment no cut-point was determined or applied, and the results are reported as %B/T.

Drug concentration samples were obtained to support an alternative format for immunogenicity testing (bridging ELISA). With the use of a RIPA format, drug concentration testing is not required.

Assessment of total antibody positive samples for the presence of neutralizing antibodies will be conducted at the discretion of the clinical team.

7.3.2. Antibodies against Host Cell Protein Antibodies (anti-HCP)

The multi-tiered sample analysis approach for immunogenicity testing will also be employed for the detection of antibodies directed against host cell proteins present in the drug product. In keeping with the multi-tiered sample analysis recommendations for immunogenicity testing, the assay design employed screening (no inhibition), confirmatory (competitive inhibition with excess HCP), and titer tiers. However, since a high positive rate of pre-existing antibodies is anticipated due to ubiquitous exposure of the general population to yeast proteins, sample analysis is limited to the screening and confirmatory tiers. Relative anti-HCP antibody levels over time will be estimated using sample ECL response in the screening assay.

The assay employed for anti-HCP antibody evaluation will be fully validated using a surrogate positive control antibody, developed from host cell protein antigens (Pichia pastoris). Host antigens for the reference product (from the host Escherichia coli K12) are not available to develop a parallel assay for Lantus anti–HCP antibodies. In order to maintain blinded analysis, both treatment arms will be evaluated with the assay. Any change in the sample analysis method will be mentioned in the sample analysis plan.

7.4 Safety Assessments

7.4.1. Medical History

Medical history will be recorded at randomization and must include any clinically relevant prior diagnosis, concomitant diseases and abnormalities, documentation of drug allergies, prior systemic and local allergic reactions to insulin. The medical history should be checked against the inclusion and exclusion criteria.

7.4.2. Prior and Concomitant Medication

All treatments being taken by the patients at the time of randomization and all treatments given in addition to the trial treatment (investigational products), are regarded as concomitant treatments and must be documented in the eCRF.

During the extension study the Investigator should ensure that no medications listed in Table 2 are initiated.

7.4.3. Vital Signs

Vital signs are body temperature, respiratory rate, sitting pulse, and blood pressure (both systolic and diastolic). The patient should be resting in sitting position for at least 5 minutes before the measurements are performed. The vital signs will be recorded as specified in the SCHEDULE OF ACTIVITIES.

7.4.4. Physical Examination

Complete physical examination data will be recorded as specified in the SCHEDULE OF ACTIVITIES and will include the following assessments: general appearance, head, ears, eyes, nose and throat (including thyroid), skin, respiratory system, cardiovascular system, abdomen, lymph nodes, musculoskeletal system, gastrointestinal system (including mouth) and neurological system; and a diabetic foot examination.

7.4.5. Electrocardiogram

A 12-lead ECG will be done as specified in the SCHEDULE OF ACTIVITIES. The ECG will be performed in supine position after at least 5 minutes resting in the supine position. The results will be assessed qualitatively as normal or as abnormal with the abnormalities specified.

7.4.6. Local and Systemic Allergic Reactions

Local and systemic allergic reactions will be recorded as specified in the SCHEDULE OF ACTIVITIES. The Investigator should ask the patient at each trial visit about allergic reactions and check the injection site(s) for possible local allergic reactions.

If a patient develops any type of allergic reaction, routine evaluations for identifying the cause and type of allergic reaction need to be done. These may include skin biopsy, blood sample collection for further testing, skin tests for detecting allergens or other standard methods considered essential by the Investigator.

7.4.7. Adverse Events and Serious Adverse Events

Adverse events and SAEs will be recorded as specified in the SCHEDULE OF ACTIVITIES from the time of signing the informed consent form until the end of the follow-up visit. After the follow-up visit, any SAEs reported by the patients will be recorded if they are deemed related to trial drugs by the Investigator.

7.4.8. Hypoglycemic Events

Patients will be instructed to record all hypoglycemic events in the patient diary from week 0 through the EOT visit. The hypoglycemic events will be reviewed by the Investigator and transcribed into the eCRF by the Investigator or designee after the diary has been collected. Details of the different types of hypoglycemic events are provided in section 7.5.6.1. Severe and serious hypoglycemic episodes will be reported to the sponsor immediately, according to section 8.3.2.8.

7.4.9. Safety Related to Device Use

Adverse events could potentially result from device failure or user error. These safety issues will be identified, documented, investigated and if appropriate, reported. Any SAE associated with a device issue will be reported to the sponsor immediately according to section 8.3.2.8.

7.4.9.1. Adverse Events Associated with Device and Device Complaints

All AEs associated with the device will be captured according to section 8.3, including an assessment of causality by the Investigator. Any device-related complaints will be investigated at the discretion of the sponsor.

7.4.9.2. Investigator's Responsibility

- During enrollment, patients will be instructed to document in their diary and inform the Investigator (during the next scheduled visit) about any difficulties encountered during the administration of the drug.
- Patients will be instructed to immediately report to the Investigator any suspected failure of the device to deliver the intended dose, or an SAE associated with the device.
- For AEs associated with use of the device, the Investigator will record the AE term in the eCRF to capture both the adverse consequence as well as the association with the device (e.g. injection site pain from accidental needle stick).
- The Investigator will record in the eCRF whether or not the device issue resulted in an AE; an assessment of whether the AE was related to the drug, the device, or both; and any other relevant information about the patient's condition.
- Any device-related complaint resulting in an SAE will be reported to Mylan within 24 hours (per section 8.3.2.8).
- Even in the absence of a report by the patient of device failure or a device related AE, if the Investigator sees that the pen is broken/damaged or disassembled, the Investigator will replace the device and send the damaged device to the CRO/Mylan.

7.4.9.3. Sponsor's Responsibility

- For SAEs, Mylan will independently evaluate whether the SAE was drug-related or related to an adverse device effect.
- In the event that the information available in the eCRF is inadequate for root cause analysis, Mylan will send a questionnaire to the Investigator, asking for more details.
- All SAEs related to the use of the needle, which is a legally marketed device, will be recorded and reported to Mylan for investigation and reporting to the needle manufacturer, if deemed necessary, based on the outcome of the investigation.
- Information regarding the circumstances, evaluation, investigation and analysis of all device deficiencies will be included in the clinical study report (CSR).

7.4.10. Safety Laboratory Assessments

Safety and efficacy laboratory assessments will be performed by the following central laboratory:

Table 5: Central Laboratory Details for Safety Sample Shipment

Samples from Europe will be sent to	Q^2 (Squared) Solutions The Alba Campus, Rosebank Livingston, EH54 7EG UK
Samples from US will be sent to	Q^2 (Squared) Solutions27027 Tourney Road, Suite 2E Valencia, CA 91355 USA

7.4.10.1. Hematology, Blood Chemistry, and Urine Analysis

Blood samples for hematology, blood chemistry, and urine samples for urine analysis will be collected and analyzed as specified in the SCHEDULE OF ACTIVITIES.

Hematology panel includes hemoglobin, hematocrit, white blood cell count with differentials, red blood cell count with indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration) and platelet count.

Blood chemistry panel includes blood urea / BUN, serum creatinine, creatinine kinase, uric acid, serum bilirubin (total and direct), total protein, serum albumin, ALT, AST, alkaline phosphatase, LDH, lipase, sodium, potassium, calcium, magnesium, chloride, and bicarbonate.

For the urinalysis a routine urine dip will be performed by the site using supplies provided by the central laboratory. This will include assessment of specific gravity, pH, and semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood. If the Investigators want to do detailed urine testing, the site will send a urine sample to the central laboratory for microscopic evaluation. Microscopic examination will include WBC, RBC, casts, cast type, crystals, epithelial cells, renal cells, mucus threads, bacteria, yeast, and *Trichomonas*.

7.4.10.2. Fasting Lipid Profile

Blood samples for fasting lipid profiles will be collected and analyzed as specified in the SCHEDULE OF ACTIVITIES. The lipid profile includes total cholesterol, high density lipoprotein (HDL), LDL and triglycerides. For this protocol 'fasting' will be defined as no intake of food or drink (except water) for at least 10 hours.

7.5 Other Assessments

7.5.1. Demographic Variables

Demographic variables will be documented at visit 1 and include date of birth (in Germany, only age OR year of birth), gender and race (Asian, American Indian, Alaska Native, Black, Caucasian, Hispanic, Native Hawaiian, Hispanic, others).

7.5.2. Pregnancy Test

Pregnancy tests will be performed as specified in the SCHEDULE OF ACTIVITIES. Sites will receive test strips for the urine pregnancy tests from the central laboratory. The result of the urine pregnancy test must be available before trial medication is dispensed. During the week 0, visit 1, the medication will be dispensed after confirming the urine pregnancy test performed during EOT visit of MYL-GAI-3001 study is negative.

7.5.3. Study Treatment Non-Compliance

Patients will be identified as study treatment non-compliant if they meet any of the following criteria:

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

7.5.4. Dilated Ophthalmoscopy / retinal photography

Dilated Ophthalmoscopy / Retinal photography testing should be performed once within one of the visits during the 28 days of enrolment.

7.5.5. Patient Diary

Patients will receive patient diaries as specified in the SCHEDULE OF ACTIVITIES. The following will be recorded by the patient in the diary:

- Results of the 8-point SMBG measurements (on 3 days in the week before the next visit, of which 2 should be consecutive days)
- Mylan's insulin glargine/Lantus® and mealtime insulin doses on days where a 8-point SMBG is performed
- Hypoglycemic events experienced by the patient
- Adverse events experienced by the patient
- Disposable pen and needle -related issues

The Investigator will instruct the patient on the recording and measurement in detail of these assessments and will review the diary as specified in the SCHEDULE OF ACTIVITIES. During review the Investigator should assess patient compliance with the trial procedures and based on the results of the 8-point SMBG check if a dose adjustment is required. The entries in the patient diary will be transcribed into the eCRF by the Investigator or designee.

7.5.6. Hypoglycemia

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

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

7.5.6.1. 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 patient 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 patient 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 a serious adverse event. Other hypoglycemic episodes which fulfils ICH criteria for seriousness (life-threatening, hospitalization etc.) or represent important medical events based on Investigator's judgment should also be reported to sponsor within 24 hours.

7.5.6.2. 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.

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

7.5.6.3. Management of Hypoglycemia

The following steps are recommended for managing hypoglycemic episodes:

1. The patient 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 patient 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, 4/5 cup of juice or regular soft drink, 4-5 glucose tablets).
3. Patient 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, patients should follow with additional carbohydrate or a snack.

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

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

For an event of severe hypoglycemia the patient 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 patient 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 different subtypes (Refer to section 7.5.6.1).

7.5.6.4. Reporting of hypoglycemic episodes

Hypoglycemic events and any associated symptoms are recorded only on the hypoglycemic episodes page of the CRF. Severe hypoglycemia and those episodes meeting any of the ICH seriousness criteria (section 8.2.4) are also to be notified as SAEs to the Mylan Global Product Safety and Risk Management department, as described in section 8.3.2.8; and entered on the SAE and AE pages.

8. ADVERSE EVENT REPORTING

8.1 Adverse events

All observed or patient-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 term "Mylan" includes Mylan's designated representative). The Investigator is required to assess causality and should obtain sufficient information to determine the causality of all AEs. All AEs will be followed till 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.

8.2 Definitions

8.2.1. 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 (reported at time of randomization in medical history) will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition.

Events occurring in patients treated with the active comparator are also considered AEs. An AE will be defined as a treatment-emergent adverse event (TEAE) if the first onset (or worsening, in the case of pre-existing disease) is after the first administration of Mylan's insulin glargine or Lantus® after randomization through follow-up visit or 28 days after last dose [for patients that do not have a follow-up visit].

8.2.2. Adverse Drug Reaction

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

either the reporting Investigator or the sponsor as having a reasonable causal relationship to an investigational product will be designated as ADRs.

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

8.2.3. 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 trial. 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 Mylan's insulin glargine is the Investigator's Brochure. The reference safety documents for Lantus® will be the current US prescribing information [7].

8.2.4. 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 trial drug during pregnancy is considered an SAE. However, a newly diagnosed pregnancy in a patient that has received the trial drug is not considered an SAE unless it is suspected that the trial drug interacted with a contraceptive method and led to the pregnancy. The patient with newly

diagnosed pregnancy will discontinue receiving trial 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 trial 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 trial.

8.3 Management of Adverse Events

AEs or SAEs will be collected from the time the patient signs the informed consent form until the end of the follow-up visit or phone-visit. Pre-existing diseases or conditions (reported at visit 1 in medical history) will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality of the disease or condition. An SAE deemed related to the trial drug by the Investigator in consultation with sponsor will be reported even after the follow-up visit if reported by patients. AEs and SAEs would also be recorded at phone calls. All SAEs should be immediately (within 24 hours) reported as per Section 8.3.2.8.

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

8.3.2. Evaluation

8.3.2.1. Severity Assessment of Adverse Events

The clinical severity of an AE will be graded using the NCI-CTCAE Criteria Version 4.03. A copy of these criteria will be provided to each trial 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 patient's usual function.
Grade 2 – MODERATE	Interferes to some extent with patient's usual function.
Grade 3 – SEVERE	Interferes significantly with patient's usual function.
Grade 4 - LIFE-THREATENING	Risk of death at time of event
Grade 5 – DEATH	Death related to AE

If an AE is graded 4 or 5 according to the above criteria, then the AE meets the criteria for an SAE and the Investigator should immediately notify the sponsor or designee as described in section 8.3.2.8.

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 8.2.4.

8.3.2.2. 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 after study medication was permanently withdrawn or patient completed the treatment period.

8.3.2.3. 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 patient'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.

8.3.2.4. Causality Assessment of Adverse Events

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

In addition, if the Investigator determines an AE or SAE is associated with trial 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 trial 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 trial treatment in accordance with the following definitions:

Table 8: Definition of Suspected Relationship between the Events and Trial 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 reasonable related	For Example: Event or laboratory test abnormality,

	although a causal relationship cannot be ruled out	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

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

8.3.2.5. Documentation

All AEs occurring within the period of observation for the trial must be documented in the CRF with the following information; where appropriate (the period of observation for the study is described in Section 8.3):

- 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 trial medication as a result of AE.
- Outcome.
- Investigator's opinion regarding the AE relationship to the trial treatments.

Hypoglycemic events and associated signs/symptoms will only be recorded on the hypoglycemic episodes page of the CRF, unless they are SAEs.

8.3.2.6. Treatment of Adverse Events

AEs that occur during the trial 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 trial treatment. The decision about whether the patient may resume the trial treatment will be made by the sponsor after consultation with the Investigator and/or medical monitor.

8.3.2.7. Follow-up

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

8.3.2.8. Notification

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

The SAE reporting form (paper form only) 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). Patient 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 patient's trial 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 (trial site and Investigator)
- Suspected trial treatment
- Patient's trial number
- SAE term
- The seriousness criteria that were met
- Investigator's opinion of the relationship to the trial treatments
- Severity

- Patient's age
- Date of first dose of trial treatment
- Date of last dose of trial treatment, if applicable
- Start and stop (if applicable) of the event (date and time)
- A brief description of the event, outcome to date, and any actions taken
- Concomitant medication at onset of the event
- Relevant past history information
- Relevant laboratory test findings

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

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

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

Sponsor Contact Information for Immediately Reportable Events

Email is the preferred method of communication.

All SAEs must be notified within 24 hours to:

Global Product Safety & Risk Management, Mylan

PV MAIL HUB FOR IMMEDIATE SAFETY REPORTS:

pvclinical@mylan.com

In case an acknowledgment is not received within 24 hours, forward via

Fax +1.304.285.6409

8.3.2.9. 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.

8.4 Special Situations

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

8.4.1. Pregnancy

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

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

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

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

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

8.4.2. 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.

8.5 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 trial drug administration or that are present at baseline and worsen following the administration of trial 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 trial dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the trial, additional concomitant drug treatment, or other therapy; and/or
- The test result is considered to be an AE by the Investigator or sponsor.

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

Approximately 138patients with type 1 diabetes will participate in this trial. Approximately 69 patients will be randomized to one of the two sequence groups (Mylan sequence group: Mylan's insulin glargine switch to Lantus® sequence group and switch back to Mylan's insulin glargine or Lantus Sequence Group: Lantus® to Lantus® to Lantus® sequence group) in a 1:1 ratio. No replacement of patient will be performed if patient discontinued prematurely from the study. For the modified intent-to-treat (mITT) population, power to demonstrate equivalence with ±0.4% limits will be 90% with 10% patients who don't have at least one baseline and one last period HbA1c data. The power is calculated assuming no true mean group difference and a 0.61% standard deviation. This standard deviation is based on published results for clinical studies with Lantus® [12].

9.2 General Considerations

Statistical analysis of this trial will be the responsibility of Mylan or designated clinical contract organizations.

Any change to the data analysis methods will be mentioned in the statistical analysis plan. Any additional analysis, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

For the statistical analysis, baseline is visit 1, which includes the post study measurements of the main study MYL-GAI-3001.

9.2.1. Primary End Point

The HbA1c difference of change from baseline between two periods at 12 weeks from week 36. If week 36 HbA1c is missing then last non-missing values from period 3 will be used.

9.2.2. Study Population

The primary analysis will be based on the mITT population.

- The ITT population includes all randomized patients (including patients who receive incorrect treatment, do not complete the trial or do not comply with the protocol or used prohibited medication) and have baseline (week 0 visit) and at least one post-baseline value. ITT population will be used for secondary variable analyses.
- The mITT population includes all randomized patients (including patients who receive incorrect treatment, do not complete the trial or do not comply with the protocol or used prohibited medication) and have at least one baseline (week 0 visit) HbA1c value and one post-baseline HbA1c value at treatment period 3. The mITT will be used for primary analysis.
- Per Protocol (PP) population. The PP population includes patients who complete at least one baseline and one period 3 values and do not have protocol violations that impact the primary outcome. The subjects excluded from the PP population will be identified before database lock. PP population will be used for sensitivity analysis for primary variable.

- The safety population includes patients who take at least one dose of the trial medication. For safety analyses, patients will be categorized according to the treatment that they actually received. Safety population will be mainly used for safety population.

9.2.3. Handling Missing Values

No missing data will be imputed

9.2.4. Pooling

No data pooling will be performed.

9.2.5. Multiplicity Adjustment

No adjustment for multiplicity will be performed.

9.2.6. Statistical Methods

For primary endpoint analysis, equivalence for efficacy will be supported if the two sided 95% confidence interval for the difference of mean between two sequence groups (endpoint of change from baseline of Mylan sequence group minus endpoint of Lantus sequence) for HbA1c is within ±0.4%.

For sequence comparison analysis for continuous variables, analysis of covariance (ANCOVA) will be used (unless otherwise specified) with the terms of geographic region and sequence group as fixed effects and baseline value as covariate in the model. For continuous variables with more than one measurements within period, a repeated measures analysis employing a restricted maximum likelihood (REML)-based, mixed-effects model approach (MMRM) will be used for treatment comparison. For continuous variables without baseline value, analysis of variance will be used (unless otherwise specified). The baseline values for this study are the measurements after 52 weeks in MYL-GAI-3001. Paired t-test will be performed for change from baseline comparisons for each post-baseline visits. For categorical data analyses, Fisher's exact or Chi-squared tests will be used. All tests of treatment effects will be conducted at a two-sided alpha level of 0.05 or with 2-sided 95% confidence intervals.

9.3 Patient Disposition

The percent of randomized patients who completed the trial or discontinue early will be summarized for each sequence group. The comparison of patient discontinuations across sequence groups will be performed using the Fisher's exact test.

9.4 Protocol Violation

A list of significant protocol violations will be provided. A summary by sequence group at each period will also be provided, and sequence group comparison will be performed using the Fisher's exact test. Other protocol deviations will be listed in the appendices.

9.5 Patient Characteristics

Patient characteristics will be obtained at the week 0 visit; and will be listed and summarized by sequence group, and overall. The summaries will include descriptive statistics for continuous and categorical measures. Parameters will be compared by sequence group using a two sample t-test for continuous measures. A Pearson's chi-square test or Fisher's exact test will be used to test categorical measures. Patient characteristics include but are not limited to: age, gender, origin, race, weight, body mass index, duration of diabetes, baseline HbA1c and baseline fasting plasma glucose.

9.6 Concomitant Medication

Categorical use of concomitant medication taken by at least 10% patient and overall will be summarized by treatment. All concomitant medications used will be listed. Sequence groups will be compared by Chi-squared test.

9.7 Primary Efficacy Analysis

The primary endpoint is change from baseline in HbA1c value at 36 weeks. ANCOVA will be performed; and the model will include region and sequence group as fixed effect and baseline value (52 weeks in MYL-GAI-3001) as covariate using mITT population. The ANCOVA will produce a 95% confidence interval for the difference between two treatment sequence groups for mean change from baseline HbA1c at endpoint. Equivalence of Mylan's insulin glargine to Lantus® will be established if the 95% confidence interval is within ±0.4% equivalence limits. Descriptive statistical summaries for actual measurements and change from baseline will be displayed by visit and endpoint for each sequence group using ITT population.

In order to check the sensitivity of the result, primary analysis will be also performed on PP population using same model mentioned above.

9.8 Secondary Efficacy Analyses

In addition to the primary efficacy analysis for HbA1c, the following efficacy measures (both actual and change in values) will be summarized for each sequence at each post-baseline visits. Sequences will be compared using the MMRM ANCOVA model (similar to HbA1c analysis). The dependent variable will be the differences of change from baseline between two periods. The MMRM model will include the fixed, categorical effect of region and sequence group, visit, sequence group-by-visit interaction and the other as fixed effect terms region, and baseline value as covariates.

Descriptive statistical summaries for actual values and change from baseline will be displayed by visit and endpoint for each sequence group. ITT population will be applied to secondary efficacy analyses.

- Fasting plasma glucose;
- SMBG value: individual pre-meal, individual post-meal, individual 2-hour excursion after meal, bedtime, overall (average) pre-meal, overall post-meal, overall excursion, 4-point average (pre-meal + bedtime), and daily average;
- Daily prandial insulin, basal insulin, and total insulin dose (U/kg) for days of 8-point profiles.

9.9 Safety Analyses

Safety analysis will be based on safety population which includes all enrolled patients who take at least one dose of trial medication.

9.9.1. Treatment Exposure

Total treatment duration days will be summarized for each sequence arm. The sequence group will be compared using t-test.

9.9.2. Immunogenicity Profiles Analyses

Continuous immunogenicity variables such as cross-reacting antibodies percent binding will be analyzed using the MMRM ANCOVA model, similar to the primary and secondary efficacy analyses. The model will include the fixed, categorical effect of region and

sequence group, visit, sequence group-by-visit interaction and the other as fixed effect terms region, and baseline value as covariates. The p-value for sequence difference and 95% confidence interval will be constructed. If the normal distribution assumption is severely violated, then non-parametric analysis will be performed using Wilcoxon rank-sum test for sequence comparison.

Descriptive statistical summaries for actual measurements and change from baseline will be displayed by visit for each sequence group. For categorical variables such as ADA positive and negative, frequency table will be presented by visit for each period for each sequence. Fisher's exact test will be used for sequence comparison by visit.

9.9.3. Hypoglycemia Analyses

Hypoglycemia rate per patient per 30 days will be analyzed using MMRM ANCOVA model secondary for sequence group comparison. The model will include the fixed, categorical effect of region and sequence group, visit, sequence group-by-visit interaction and the other as fixed effect terms region, and baseline value as covariates. The p-value for sequence difference and 95% confidence interval will be constructed. The rate per patient per 30 days calculated between two visits is defined as total number of episodes between two visits divided by the number of days between the visits, multiplied by 30 days. This rate will also be calculated per patient for nocturnal hypoglycemia episodes. In case the normal distribution assumption is severely violated, then non-parametric analysis will be performed using Wilcoxon rank-sum test for sequence group comparison.

Incidence of all hypoglycemic episodes and nocturnal hypoglycemic episodes will be presented by sequence group by visit for each period. The incidence of hypoglycemic episodes during visit time period on treatment is defined as the incidence of patients with at least one hypoglycemic episode occurring within that period of time. Fisher's exact test will be used for sequence comparison by visit.

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

9.9.4. Adverse Event Analyses

The evaluation of adverse events will include assessments of TEAEs and SAEs.

The incidence of TEAEs will be summarized to include only one occurrence of a PT per patient per treatment period. If a patient reports multiple occurrences of the same PT and treatment period, then that PT will only be counted once. As with the PT, if a patient reports multiple TEAEs within the same SOC and treatment period, that SOC will only be counted once. Incidence of TEAEs will be presented by treatment sequence. The incidence of TEAE by severity and relation to study drug will also be summarized by treatment sequence. The incidence of both local and systemic allergic reaction-related TEAEs will be also summarized separately by SOC and treatment period for each sequence group. Fisher's exact test will be used for sequence comparison by visits.

9.9.5. Vital Signs

Change from baseline for vital signs will be analyzed using MMRM method similar to the secondary efficacy variables the ANCOVA model for sequence group comparison. The model will include the fixed, categorical effect of region and sequence group, visit, sequence group-by-visit interaction and the other as fixed effect terms region, and baseline value as covariates. The p-value for sequence difference and 95% confidence interval will be constructed using the same model for the combined periods. The summary statistics including actual measurement and change from baseline will be displayed at each visit for each sequence group.

9.9.6. Laboratory Measurement

Change from baseline for laboratory evaluations will be analyzed using similar ANCOVA model for primary analysis for treatment sequence comparison. The summary statistics including actual measurement and change from baseline will be displayed at each visit for each sequence group.

9.9.7. ECG

Summary of frequency table of percentage of patients in categories such as abnormal/non-clinically significant and abnormal/clinically significant will be presented by visit and sequence group.

9.9.8. Device Safety Assessment

The total incidence of device-related safety events will be summarized with each sequence arms, per treatment arm, at each period both for device-related TEAEs and for events related to device complaints or failures.

9.10 Subgroup Analyses

No subgroup analysis will be planned.

10. QUALITY CONTROL AND QUALITY ASSURANCE

This trial will be audited by the sponsor or sponsor's designees to check compliance with GCP guidelines. The sponsor or designee may conduct audits on any selected trial sites, requiring access to patient notes, trial documentation, and facilities or laboratories used for the trial.

Monitoring and auditing procedures are described in the following sections.

10.1 Study Monitoring

Before the start of the trial at a study site, an initiation visit or phone call will be conducted by the monitor. During the trial the monitor will visit the site to review the implementation of the center's processes associated with but not limited to:

- Completion, consistency, and accuracy of entries in the eCRFs
- Source data verification
- Progress of enrollment
- Adherence to the protocol and to GCP
- Proper storage, dispensing, and accounting of trial medication as specified in the protocol

The Investigator and key site personnel must be available to assist the monitor during these visits.

The Investigator must maintain source documents for each patient in the trial, as well as other trial documents, as specified in section 11.2. No patient identification information will leave the trial center.

In the case of electronic health records, the Investigator must give the monitor access to all relevant source documents to confirm consistency with the eCRF entries. Monitoring will be performed according to the monitoring plan for this trial.

The Investigator (or his or her staff) is responsible for completing the eCRFs and the monitor is responsible for reviewing them and for clarifying and assisting in resolving any data queries.

10.2 Audits and Inspections

Quality assurance personnel may conduct audits to evaluate compliance with the principles of GCP.

If an inspection is requested by a regulatory authority or competent authority (during the trial or after its completion), the Investigator must inform the sponsor immediately.

If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. Participation as an Investigator in this trial implies acceptance of potential inspection by regulatory authorities.

11. DATA HANDLING AND RECORD KEEPING

11.1 Electronic Case Report Forms

Before a trial is initiated the sponsor's representative will review the protocol and eCRF with the Investigators and the study staff.

By signing the Investigator's Agreement, the Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all patients who sign an ICF.

Investigator sites will be provided with access to the eCRF system, which has been fully validated and conforms to 21 Code of Federal Regulations Part 11 requirements. The site staff will be trained on the use of the eCRF including trial specific details before they are able to enter the trial data. Investigational staff will not be given access to the eCRF until they have been trained and assessed as competent to use the system.

Designated investigational staff will enter all requested information (including information entered into the diaries by the patients) required by the protocol into the eCRFs.

To ensure data accuracy, eCRF data for individual patient visits should be completed as soon as possible after the visit. Automated data validation software will check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigational staff. The monitor will perform data verification and will document this electronically in the eCRFs. The Investigator or designee must certify that data are complete and accurate within the system by providing electronic approval of the eCRF pages. A reasonable explanation must be given by the Investigator or authorized staff for all missing data. Queries will be sent to the investigational site through the eCRF system. Designated Investigator site staff are required to respond to the queries and make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the WHO Drug Dictionary, which employs the Anatomical Therapeutic Chemical classification system. Medical history or current medical conditions and AEs will be coded using MedDRA terminology.

Corresponding source documentation must support all information recorded in the eCRF. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the sponsor or designee. Laboratory results will be provided to the trial site and should be retained with each patient's source data.

11.2 Record Retention

Data on patients collected on eCRFs will be documented in an anonymous fashion and the patient will only be identified by the patient number.

At the end of the trial, the Investigator will receive a copy of the data entered into the eCRF for his or her site. The Investigator will retain the study documents for at least 15 years or as per local laws (whichever is longer). At the end of that period, the Investigator shall notify the sponsor in writing of her/his intent to destroy all such material. The sponsor shall have 30 days to respond to the Investigator's notice; the sponsor may request that the site retains

the materials for a longer duration, at the sponsor's expense. Source documents should be retained according to local laws and institution requirements.

11.3 Data Confidentiality

All data generated from the trial will be regarded as confidential. The monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the patient's original medical records for verification of trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the patient or the patient's legally acceptable representative will be authorizing such access. The records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential. All data (whether medical or laboratory) generated in the course of the trial will remain the property of the sponsor.

11.4 Source Data Access

Direct access to source data or documents will be permitted during trial-related monitoring, audits, IRB/IEC review and regulatory inspection(s).

11.5 Responsibilities Related to Devices

11.5.1. Investigator Records and Reports (See Appendix V - Letter of Approval of Pen Use by the Investigator)

According to the 21 CFR 812.140 and 150 a participating Investigator shall maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation:

- Record of receipt, use or disposition of a device that relate to:
  - The type and quantity of the device, the dates of its receipt, and the batch number or code mark
  - The names of all persons who received, used, or disposed of each device
  - Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
- Documents evidencing informed consent and, for any use of a device by the Investigator without informed consent, any written concurrence of a licensed

physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each patient shall document that informed consent was obtained prior to participation in the trial.

- An Investigator shall prepare and submit the following complete, accurate, and timely reports:
  - An Investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.
  - An Investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation.
  - If an Investigator uses a device without obtaining informed consent, the Investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
  - An Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Please see **Appendix V** for instructions regarding the prohibition of promotion and other practices and a format for the letter of approval of pen use by the Investigator (for US sites only).

12. PROTOCOL AMENDMENTS, DEVIATIONS AND COMPLIANCE

Investigators should ascertain that they will apply due diligence to avoid protocol deviations. No waivers to the protocol will be given by the sponsor.

All significant protocol deviations will be recorded and reported in the CSR main body. These will include variable deviations, for example:

1. Patient not meeting selection criteria but still included in the study
2. Patient continued in the study despite meeting study discontinuation criteria
3. Failure to perform tests or procedures which will impact the interpretation of key endpoints (e.g. safety, efficacy, immunogenicity endpoints) of the study
4. Patient not following treatment regimen mentioned in the protocol

5. Patient taking medications which are prohibited by the protocol, or can have impact on key endpoints of the study
6. GCP not followed.

With respect to inadequate documentation or conduct of SMBG, the following rules will be followed to determine deviations:

- In any given week, if there are missing values for SMBG AND the Investigator documents that the patient is non-compliant, a protocol deviation (for that visit) will be recorded; and listed in the main body of the CSR (as well as in the CSR appendices).
- In any given week, if there are missing SMBG values without accompanying documentation of non-compliance by the Investigator, a protocol deviation (for that visit) will be recorded; but listed only in the CSR appendices, and not in the main body.

Any change to the protocol can only be made in the form of a written amendment to the trial protocol. Depending on the local regulatory requirements, the amendment must be approved by the national authority and/or IEC/IRB before the amendment is implemented.

Only amendments that are required for patient safety may be implemented prior to IEC/IRB approval.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this trial, even if this action represents a violation of the protocol. In such cases, the sponsor should be notified of this action immediately.

13. ETHICS

13.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Before the start of the study, the protocol, written ICF, and/or other appropriate documents will be submitted to and approved by the IRB/IEC and/or the competent authorities, in accordance with local legal requirements. The study will not commence until written confirmation of their approval has been received by the sponsor or designee. No clinical supplies may be sent to the study sites until the relevant approvals from the IRB/IEC and competent authorities have been obtained.

No patient may undergo any procedure solely for determining eligibility for this trial until the Investigator has received written approval by the IRB/IEC and the regulatory authority.

13.2 Ethical Conduct of the Study

The trial will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subject (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2013). In addition, the trial will be conducted in accordance with the protocol, and applicable local regulatory requirements and laws.

13.3 Patient Information and Consent

All parties will ensure protection of patients' personal information. Patient names will not be included on any forms, reports, publications, or in any other disclosures to the sponsor.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent document to be used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB/IEC and the sponsor or designee before use.

According to the Declaration of Helsinki, and ICH-GCP, patients must provide their written informed consent prior to enrollment in a clinical trial and before any protocol-specified procedures are performed. Patients must declare their consent by personally signing and dating the informed consent form (ICF).

The patient will also be informed that if she/he wishes to withdraw (see section 6.2) at any time during the trial this will not have any negative consequences to further treatment at the investigational site.

14. DEFINITION OF END OF TRIAL

The end of this trial is defined as the date of the last visit of the last patient participating in the trial (last patient out or last patient last visit). Within 90 days of the end of the clinical trial the sponsor or designee will notify the ECs and regulatory authorities on the completion / termination of the trial as required according to law and regulation.

14.1 End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and have completed the trial as stated in the regulatory application (i.e., clinical trial application [CTA]) and ethics application in the Member State). Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the trial in that Member State.

14.2 End of Trial in all Other Participating Countries

End of trial in all other participating countries is defined the date and time of the last patient (patient) last visit.

15. SPONSOR DISCONTINUATION CRITERIA

The sponsor is entitled to terminate the study:

- In case there is evidence that the safety of the trial participants is no longer assured.
- In case the 3001 study interim analysis affects the current favorable patient risk benefit relationship.

Should this be necessary, the sponsor will promptly notify the Investigators; and the Investigators will be informed of the procedures to be followed to assure that adequate consideration is given to the protection of the patient's interest.

Pursuant to law and regulation, the sponsor or Investigator will notify IRB/IECs and regulatory authorities within 15 days of premature termination of the trial, clearly explaining the reasons for premature termination. After notification, the Investigator must contact all participating patients and the hospital pharmacy (if applicable) within 30 days. Trial sites may be asked to have all patients currently participating in the trial to complete all assessments for an early termination visit. As directed by the sponsor, all trial materials must be collected and all eCRFs completed as far as possible.

A specific site may be terminated for unsatisfactory patient enrolment (as long as there are no active recruited patients), insufficient quality, or for improper data recording.

IRB/IECs and regulatory authorities may also terminate the trial prematurely for any reason and at any time following consultation with the sponsor. A decision to prematurely terminate the trial is binding on all Investigators.

16. PUBLICATION OF STUDY RESULTS

Information generated by the trial is the property of the sponsor. Publication or other public presentation of data resulting from this trial requires prior review and written approval of the sponsor.

16.1 Communication of Study Results

This trial will be registered on ClinicalTrials.gov, the EudraCT database and in other trial registries as deemed appropriate. The basic results will be posted at www.clinicaltrials.gov in a tabular format within a year from the end of the trial (as defined in the preceding sections) or upon finalization of the CSR, whichever occurs later.

The trial results will be documented in a clinical study report (CSR), in an ICH E3-compliant format. A copy of the final report, duly checked for correctness, completeness, integrity, and accurate representation of data and interpretation of trial outcome, will be issued to Investigators and counter-signed by the global coordinating Investigator; as per the sponsor's SOPs.

16.2 Publications by Investigators

For all publications relating to the trial, institutions will comply with recognized ethical standards concerning publications and authorship, including *Section II - "Ethical Considerations in the Conduct and Reporting of Research"* of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Data from individual trial sites must not be published separately. It is agreed that the results of the trial will not be submitted for abstract, presentation, poster exhibition or publication by the Investigator until the sponsor has reviewed and commented on the presentation or manuscript for publication. Abstracts, manuscripts, and presentation materials should be

provided to the sponsor for review and approval at least 30 days prior to the relevant submission deadline.

17. REFERENCES

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18. APPENDICES

Appendix	Title
I	Questionnaire to Assess Hypoglycemia Unawareness
II	Suggested General Guidance for Insulin Dose Titration
III	4- and/or 8-point Glucose Estimation Time Points
IV	Sample Patient Diary Information
V	Letter of Approval of Pen Use by the Investigator (for US sites only)

Appendix I - Questionnaire to Assess Hypoglycemia Unawareness

Please circle only one answer for each question.

1. Have you **lost** the ability to experience symptoms such as sweating, shaking, palpitations, light-headedness, or nervousness when your blood sugar is low?

   No / Yes

2. To what extent can you recognize low blood sugar based on symptoms?

   Never / Seldom / Sometimes / Often / Always ["Never," "Seldom," or "Sometimes" = Yes]

3. Below which level do you feel that your blood sugar is low?

   65 / 60 / 55 / 50 / 45 [55 or below = Yes]

4. During the past year, did you have any low blood sugar episode associated with confusion for which you required assistance from another person?

   No / Once / More than once ["More than once" = Yes]

5. During the past year, did you have any low blood sugar episode for which you required intervention from paramedics, an emergency department visit, or an injection of glucagon by another person?

   No / Yes

Diagnosis of Hypoglycemia Unawareness (HUN)

Patients will be considered to have HUN if 3 of the 5 questions were scored "yes."

References: [8,9].

Appendix II - Suggested Guidance for Insulin Dose Titration

Lowest fasting capillary blood glucose (pre-breakfast) value for 3 days	Adjust basal insulin dose (U per dose) (Lantus® or Mylan's insulin glargine)
>270 mg/dL	+ 6 U
181-270 mg/dL	+ 4 U
151-180 mg/dL	+ 2 U
131-150 mg/dL	+ 1 U
71-130 mg/dL (Target level)	Maintain Dose
56-70 mg/dL	-2 U
<56 mg/dL	-4 U

Lowest post-prandial capillary blood glucose value (2 hour post food) for 3 days	Adjust mealtime insulin dose (U per dose) (Insulin lispro)
>270 mg/dL	+ 6 U
201-270 mg/dL	+ 4 U
180- 200 mg/dL	+ 2 U
< 180 mg/dL (Target level)	Maintain Dose

Comments:

- Titration should be performed first for the basal insulin. For elevated fasting pre-breakfast glucose levels, adjust only the basal insulin dose.
- Once basal insulin level has been titrated to optimum, then mealtime insulin should be titrated.
- Post-prandial glucose levels are estimated 2 hours after the start of the respective food intake.
- Apart from glucose levels, the dose of mealtime insulin should be guided by expected carbohydrate content of the next meal, and expected level of physical activity within next 4-6 hours. If meal is skipped, the dose should be skipped.
- The target should be the lower limit of the range mentioned above, so that the final value will remain in the expected range.

Appendix III - 4-Point and/or 8-Point Glucose Estimation Time Points

Time of the day	Specific point (8-point)	Specific point (4-point)
Fasting Before breakfast	1	1
2 hours after breakfast	2	
Before lunch	3	2
2 hours after lunch	4	
Before dinner	5	3
2 hours after dinner	6	
Just before sleep	7	4
At 3±1 AM	8	

Comments:

- Specific days on which the SMBG need to be estimated is as mentioned in the **Assessment Schedule**.
- On all days in which SMBG is not mandated by protocol, patients will be advised to self-monitor blood glucose 4 times a day as per standard of care in type 1 diabetes.
- The 8th point time can be adapted for patients on night shift (in discussion with the Investigator) to approximately 4 hours after going to bed.

Appendix IV - Sample Patient Diary Information

- Trial, site and patient identification information
- Results of 8-point SMBGs performed as per protocol
- Insulin dose information on days where 8-point SMBGs are performed
- Details of hypoglycemic events
- Details of untoward experiences (AEs)
- Details of problems with the disposable pens or needles

Appendix V - Letter of Approval of Pen Use by the Investigator (for US Sites only)

Prohibition of Promotion and Other Practices

According to the 21 CFR 812.7, an Investigator or any person acting for or on behalf of a sponsor or Investigator shall not:

- Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.
- Commercialize an investigational device by charging the patients or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.
- Unduly prolong an investigation. If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation.
- Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

The format below should be followed for the letter of approval.

The protocol identification code for the study in the IND	
Name and address of the Investigator	
The name and address of the sub-Investigators who will be assisting the Investigator in the conduct of the study	
The name and address of the medical school, hospital or other research facility where the clinical investigations will be conducted	
The name and address of the clinical laboratory facilities to be used in the study	
The name and address of the institutional review board that is responsible for review and approval of the study	

1. I have gone through the protocol and agree to conduct the study as mentioned in the protocol
2. I have sufficient education, training and experience in the clinical investigation of the drug using the new device.
3. I shall maintain the following accurate, complete, and current records relating to the my participation in the investigation:

- Record of receipt, use or disposition of a device that relate to:
  - The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
  - The names of all persons who received, used, or disposed of each device.
  - Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
- Documents evidencing informed consent and, for any use of a device by the Investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

4. I shall prepare and submit the following complete, accurate, and timely reports:
   - I shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.
   - I shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of my part of an investigation.
   - If I use a device without obtaining consent form, I shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
   - I shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.
5. I shall not:

- Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.
- Commercialize an investigational device by charging the patients or Investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.
- Unduly prolong an investigation. If data developed by the investigation indicate in the case of

a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation.

- Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

The details of Mylan's insulin glargine pen have been provided to me. I have gone through the detailed literature, label, and the user information. I am aware that the disposable pen planned for the study is not yet approved by FDA. I approve the use of the Mylan non-cleared, disposable pen injector for this study based on the device posing no significant risk to the patient.

Signature and date

INVESTIGATOR AGREEMENT PAGE

PROTOCOL #	VERSION	PROTOCOL TITLE	EFFECTIVE DATE
MYL-1501D-3003	2.0	An Open-label, Randomized, Multi-center, Parallel-Group Clinical Trial Comparing the Efficacy and Safety of Mylan's Insulin Glargine with Lantus® in Type 1 Diabetes Mellitus Patients-An Extension Study.	06-May-2016

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Quintiles and Mylan.
- Not to implement any changes to the protocol without agreement from the Sponsor and prior review and written approval from the Competent Authority and/or Independent Ethics Committee (IEC)/Institutional Review Board (IRB), as applicable, except where necessary to eliminate an immediate hazard to the patients.
- That I am thoroughly familiar with the appropriate use of the investigational product(s) as described in this protocol, and any other information provided by the Sponsor, including but not limited to the following: the current Investigator's Brochure (IB) or equivalent document.
- That I will comply with the revised Declaration of Helsinki (2013), the International Conference on Harmonisation Guidelines on Good Clinical Practice (ICH-GCP), and other applicable regulations and guidelines for the conduct of clinical trials.
- To ensure that all persons assisting me with the study are adequately informed about the investigational product(s) and of their study-related duties and functions as described in the protocol.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about each Investigator's proprietary interest in the Sponsor or the investigational product, and, more generally, about each Investigator's financial ties with the Sponsor. Mylan will use and disclose the information solely to comply with regulatory requirements. Hence, I agree:
  - To supply Mylan with any necessary information regarding proprietary interest and financial ties (including those of my spouse and dependent children);
  - To promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
  - That Mylan may disclose to regulatory authorities any information it has about such proprietary interests and financial ties.

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Investigator's Signature Date

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Name and Title of Investigator *(typed or printed)*