

AMENDED CLINICAL TRIAL PROTOCOL 01

COMPOUND: Toujeo / insulin glargine 300 units/ml – HOE901

A randomized, open-label, parallel group real world pragmatic trial to assess the clinical and health outcomes of Toujeo® compared to commercially available basal insulins for initiation of therapy in insulin naïve patients with uncontrolled type 2 diabetes mellitus

STUDY NUMBER: LPS14347

STUDY NAME: Achieve Control Real Life Study Program

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CLINICAL TRIAL SUMMARY

COMPOUND: Toujeo (insulin glargine 300 units/ml) – HOE901	STUDY No: LPS14347 STUDY NAME: Achieve Control Real Life Study Program
TITLE	A randomized, open-label, parallel group real world pragmatic trial to assess the clinical and health outcomes of Toujeo® compared to commercially available basal insulins for initiation of therapy in insulin naïve patients with uncontrolled type 2 diabetes mellitus
INVESTIGATOR/TRIAL LOCATION	US, Canada
PHASE OF DEVELOPMENT	Phase IV
STUDY OBJECTIVE(S)	<p>Primary Objective</p> <ul style="list-style-type: none"> • Demonstrate clinical benefit of Toujeo in achieving individualized HEDIS HbA1c targets (<8% if age ≥ 65 years or with defined comorbidities (as listed in Appendix G) or otherwise <7%) at 6 months without documented symptomatic (BG ≤ 70mg/dl) or severe hypoglycemia at any time of day from baseline to 6 months in uncontrolled insulin naïve patients with type 2 diabetes initiating basal insulin therapy in a real world setting. <p>Secondary Objectives</p> <p>Secondary objectives are to compare Toujeo to other commercially available basal insulins at 6 and 12 months after initiating insulin therapy in a real world setting in terms of:</p> <ul style="list-style-type: none"> • Patient persistence with assigned basal insulin therapy, • Risk of hypoglycemia including the incidence and rate of documented symptomatic and severe hypoglycemia, • Changes in HbA1c, fasting plasma glucose, body weight, • Differences in patient and provider reported outcomes (including Diabetes Treatment Satisfaction Questionnaire Status and Change Versions [DTSQs and DTSQc]), Hypoglycemia Patient Questionnaire, and patient and provider reported Global Effectiveness Scale (GES), • Healthcare resource utilization including hospitalizations and emergency department or other provider visits and healthcare costs.
STUDY DESIGN	<p>Potential study patients within designated practice sites who meet eligibility criteria may be identified by review of either payer or provider data bases. The inclusion/exclusion criteria will be applied to relevant databases to identify appropriate subjects with 12 months of baseline medical data available and who had actively sought care at the site in the last 12 months.</p> <p>Achieve Control includes a planning phase and the prospective study phase. During the planning phase of the trial, payer, research organization, and HCP databases are reviewed to identify appropriate sites and patients eligible for the study. Patients may also be identified through ongoing review of these databases including at the site level on an ongoing basis during the trial. Patients will be screened at the practice site to determine eligibility for study enrollment. Patients will be assigned to one of two treatment groups using a</p>

	<p>patient-level randomization. Given the potential impact of certain variables on the primary endpoint, randomization will be stratified by individualized HbA1c target (<8%/<7%), SU use ever (y/n), GLP-1 RA use ever (y/n) and baseline HbA1c (<9%/≥9%).</p> <p>The two treatment arms of the study will be:</p> <ol style="list-style-type: none"> 1) Toujeo with its available patient support program, 2) Commercially available insulin detemir (Levemir®) or insulin glargine-U100 (Lantus®) with or without a patient support program. <p>Randomization will be 1:1 between the two arms of the study and the choice of comparator basal insulin will be based on the usual practice at the clinical site and not by randomization.</p> <p>The study will include a 6 month treatment period ending in assessment of the primary and secondary endpoints followed by a 6 month extension period for assessment of certain additional endpoints. It will also include an interim analysis (IA) for overwhelming efficacy on the primary endpoint, planned to be conducted when approximately 1800 patients have been randomized and completed their 6-month visit. If the targeted sample size (1800) cannot be reached, it could be considered to include a lower number of patients, however not below 1700. In this case, the nominal significance level to be spent at interim and at final 6-month analyses would be recalculated accordingly before the database lock for IA.</p> <p>An independent Data Monitoring Committee (DMC) will review data from this IA.</p> <p>Dose regimen: Patients will be initiated on basal insulin therapy per the prescribing instructions for each insulin and titrated to a target fasting glucose consistent with the individualized HbA1c target according to the typical protocol used at each site and investigator discretion.</p> <p>Financial support will be provided by Sanofi for the cost of commercially available basal insulin as well as for Toujeo.</p> <p>Collection of hypoglycemia events and symptoms:</p> <p>A glucometer with wireless data transmission capabilities will be used to collect self-measured plasma glucose (SMPG) including SMPG associated with hypoglycemic symptoms. An electronic diary (eDiary) will be used to record the symptoms of hypoglycemia and other relevant clinical information.</p>
<p>STUDY POPULATION</p> <p>Main selection criteria</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients with T2DM, as defined by the ADA/WHO, diagnosed for at least 1 year at the time of the screening visit, insufficiently controlled after at least 1 year of treatment with 2 or more of the following: oral agents (metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, or SGLT-2 inhibitors) or GLP-1 receptor agonists for daily use and approved for use with insulin (Victoza®, Byetta®, Adlyxin®). • Adult patients who have signed an Informed Consent Form and Health Insurance Portability and Accountability Act (HIPAA) Authorization Form <p>Exclusion criteria</p> <ul style="list-style-type: none"> • HbA1c <8.0% or >11.0%, • Males or females <18 years of age, • Type 1 diabetes mellitus,

	<ul style="list-style-type: none"> Any clinically significant abnormality identified on physical examination, laboratory tests, or vital signs at the time of screening, or any major systemic disease resulting in short life expectancy that in the opinion of the Investigator would restrict or limit the patient's successful participation for the duration of the study, Use of any product containing insulin (Lantus, Levemir, Humulin®, Novolin®, Humalog®, Novolog®, Apidra®, Afrezza®, Toujeo®, Tresiba®) since the time of diagnosis with T2DM prior to the time of screening other than temporary use such as during a pregnancy or hospitalization or short term outpatient use (≤10 days) during an acute medical event, Use of oral hypoglycemic agents other than those noted in the inclusion criteria; GLP-1 receptor agonists for weekly use (Trulicity®, Tanzeum®, Bydureon®), or not approved for use with insulin, or any investigational agent (drug, biologic, device) within 3 months prior to the time of screening, All contraindications to commercially available insulin therapy or warnings/precautions of use as displayed in the respective national product labeling for these products, Pregnancy or lactation, Women of childbearing potential with no effective contraceptive method.
Total expected number of patients	3324 patients (1662 per arm), 160 from Canada Approximately 439 sites in US, 20 sites in Canada
STUDY TREATMENT(s)	
Investigational medicinal product(s) Formulation	Tested Drug: Toujeo/HOE901-U300 will be commercially available 300 U/mL insulin glargine solution for subcutaneous (sc) injection in 1.5 ml cartridges in the marketed Toujeo SoloSTAR® pen device. The disposable pen injector allows for dose setting in the range of 1-80 U with minimum dose increments of 1.0 U. Dilution or mixing of Toujeo with other insulin is not allowed. Control Drugs: Comparator basal insulins (Lantus/Levemir) will be commercially available formulations and used according to label.
Route(s) of administration	Tested drug or Control drugs: Insulin glargine given as either commercially available Toujeo/HOE901-U300 or Lantus U100 will be self-administered by sc injection once daily in the morning or evening according to label. Commercially available Levemir will be self- administered by sc injection once or twice daily in the morning or evening according to local label.

Dose regimen	<p>Tested drug or Control drugs:</p> <p>Dosing of insulin glargine given as Toujeo/HOE901-U300 or Lantus U100 and dosing of Levemir will be titrated to a target fasting glucose consistent with the individualized HbA1c target according to the typical protocol used at each site and investigator discretion.</p> <p>Initiation of the basal insulin will be done according to the label and titration will be done according to local guidelines and investigator discretion.</p> <p>The titration regimen is to be done according to real world practice and there is no recommended or forced titration in the protocol.</p>
Noninvestigational medicinal product(s) (if applicable)	Patients in both treatment groups will continue with other anti-diabetes drugs as background therapy at the discretion of the investigator and consistent with labeling guidelines for use with insulin.
Formulation	
Route(s) of administration	<p>Oral anti-diabetic agents</p> <p>GLP-1 receptor agonists for daily use which are approved for use with basal insulin and are injectable (Victoza, Byetta, Adlyxin).</p>
Dose regimen	According to label and at investigator discretion
ENDPOINT(S)	<p>Primary endpoint</p> <p>Proportion of patients with individualized HbA1c target attainment per HEDIS criteria (<8% if age ≥ 65 years or with defined comorbidities listed in Appendix G or otherwise <7%) at 6 months without documented or severe symptomatic (BG ≤ 70 mg/dl) hypoglycemia at any time of day from baseline to 6 months.</p> <p>The individual components of individualized HbA1c target attainment and absence of any documented symptomatic or severe hypoglycemia (BG ≤ 70 mg/dl) will also be evaluated as supportive analyses to evaluate consistency.</p> <p>Secondary endpoint(s)</p> <ul style="list-style-type: none"> • Change in HbA1c from baseline (obtained at screening visit within one week of study initiation) to 6 months, • Proportion of patients who remain on assigned basal insulin therapy (persistent with assigned therapy) at 6 and 12 months, • Proportion of patients with individualized HbA1c target attainment per HEDIS criteria at 6 months without documented symptomatic (BG <54 mg/dl) or severe hypoglycemia at any time of day from baseline to 6 months, • Proportion of patients with individualized HbA1c target attainment (per HEDIS criteria) at 12 months without documented symptomatic (BG ≤ 70 mg/dl) or severe hypoglycemia at any time of day from baseline to 12 months, • Proportion of patients with individualized HbA1c target attainment per HEDIS criteria at 12 months without documented symptomatic (BG <54 mg/dl) or severe hypoglycemia at any time of day from baseline to 12 months.

	<p>Patient Reported Outcomes Endpoints:</p> <ul style="list-style-type: none"> • Proportion of patient and provider reported “Excellent” or “Good” responses to GES question at 6 months and 12 months, • Average scores on total treatment satisfaction, hyperglycemia perception, and hypoglycemia perception from DTSQs at 6 months and 12 months, • Average scores on change in total treatment satisfaction, hyperglycemia perception, and hypoglycemia perception from DTSQc at 12 months, • Proportion of patients who report moderate or severe hypoglycemia since last visit on the Hypoglycemia Patient Questionnaire (questions 4 and 5) at 6 months and 12 months. <p>Healthcare Utilization Endpoints:</p> <ul style="list-style-type: none"> • Mean number and proportion of patients with hospitalizations over a 6 month and 12 month period, • Mean number and proportion of patients with emergency room visits over a 6 month and 12 month period, • Mean number of provider office visits and proportion of patients with specialty visits over a 6 month and 12 month period, • Mean overall and diabetes-related costs at 6 months and 12 months. <p>Other endpoint(s)</p> <ul style="list-style-type: none"> • Change in HbA1c from baseline to 12 months, • Change in fasting plasma glucose from baseline to 6 months and 12 months, • Change in body weight from baseline to 6 months and 12 months, • Basal insulin dose at 6 and 12 months. <p>Safety:</p> <p>Hypoglycemia will be classified in categories (Section 9.2.3.1):</p> <ul style="list-style-type: none"> • Incidence of documented symptomatic ($BG \leq 70$ mg/dl) nocturnal (0000-0559) hypoglycemia from baseline to 6 and 12 months, and 24-hour hypoglycemia from baseline to 12 months, • Rate of documented symptomatic ($BG \leq 70$ mg/dl) hypoglycemia (24 hour and nocturnal) from baseline to 6 and 12 months, • Incidence and rate of documented symptomatic ($BG < 54$) hypoglycemia (24 hour and nocturnal) from baseline to 6 and 12 months, • Incidence and rate of severe hypoglycemia (24 hour, per ADA definition) from baseline to 6 and 12 months. <p>Other safety and tolerability analyses will include adverse events and serious adverse events as well as product technical complaint events (PTC). This will include injection site reactions, hypersensitivity reactions and vital signs.</p>
ASSESSMENT SCHEDULE	See flow chart, Section 1.2

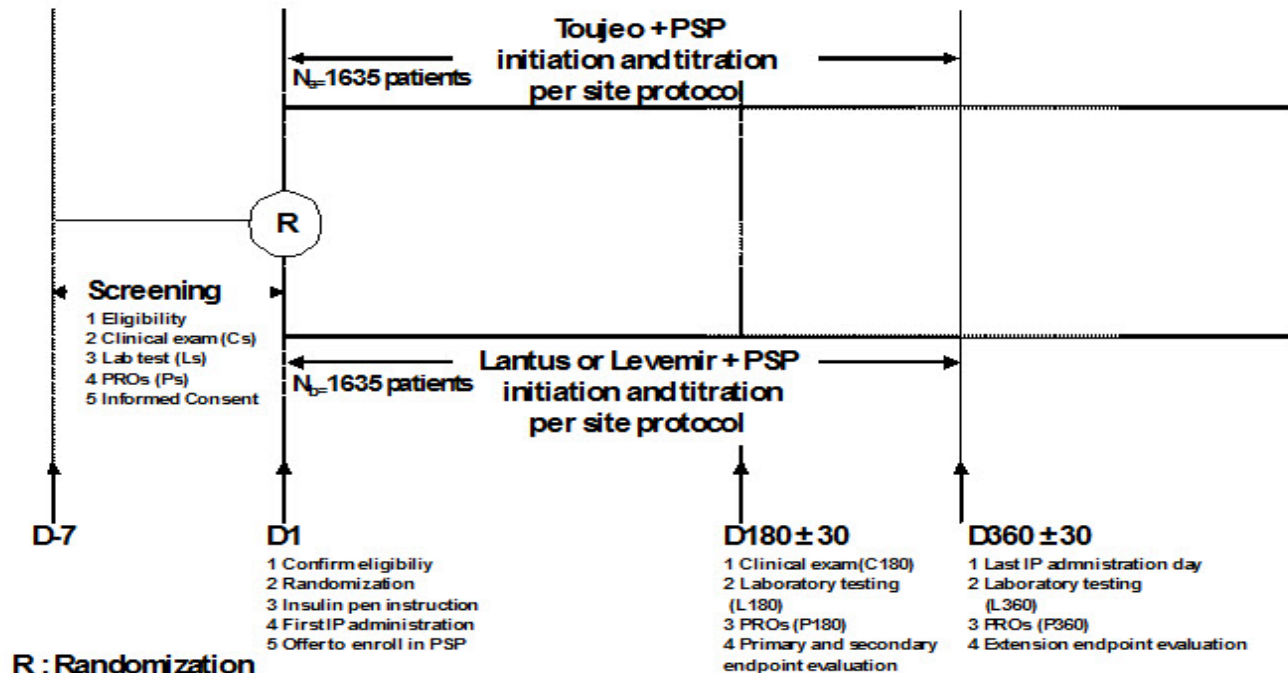
<p>STATISTICAL CONSIDERATIONS</p>	<p>Sample Size Determination:</p> <p>An original sample size of 1635 patients per treatment arm would provide at least 90% power to demonstrate superiority with an absolute difference of at least 5.5% in favor of Toujeo versus comparator basal insulins in the proportion of patients reaching individualized HbA1c target at month 6 without a documented symptomatic ($BG \leq 70$ mg/dl) or severe hypoglycemic event from baseline to month 6, assuming 30% of patients enrolled have a target HbA1c <8 per HEDIS criteria due to being older or due to the presence of medical comorbidities, and the remaining 70% having a target HbA1c $<7\%$.</p> <p>Due to the addition of the interim analysis the sample size will be increased to a total of 3324 patients (1662 patients per treatment group). The calculation takes into account one interim analysis using a group sequential approach with an efficacy boundary based on a gamma (-3) alpha spending function.</p> <p>The number of patients meeting each of these criteria will be monitored via demographic and ICD-9 data to avoid significant deviations from the assumptions above.</p> <p>The total sample size calculation of 3324 is based on the assumption of a maximum of a 33% overall (weighted average) response rate with Lantus, and at least a 5.5% increase in response rate with Toujeo, and assumes an overall 2-sided test with alpha-level 0.05 with an interim analysis performed on 1800 patients followed 6 months.</p> <p>Analysis Populations:</p> <p>The primary analysis will be performed on the Intent-To-Treat (ITT) population, which will comprise all randomized patients, irrespective of the treatment actually being received at the time of analysis.</p> <p>Safety will be assessed on an as-treated population, defined as all randomized patients who actually received at least 1 dose or part of a dose of IMP, analyzed according to the treatment actually received.</p> <p>Primary Analysis:</p> <p>The proportion of patients reaching individualized HbA1c target at 6 months without documented symptomatic ($BG \leq 70$ mg/dl) or severe hypoglycemia will be compared between treatment groups using a logistic model with log link, adjusting for individualized HbA1c target ($<8\%/<7\%$) and other stratification factors used at randomization: SU use ever (y/n), GLP-1 RA use ever (y/n), and baseline HbA1c (as continuous). As a sensitivity analysis, a multivariate analysis will be performed, adding the following baseline characteristics BMI, Patient Activation Measure (PAM) as an assessment of patient engagement, duration of diabetes and age.</p> <p>One interim analysis is planned for the purpose of overwhelming efficacy on the primary composite endpoint when 1800 patients have been randomized and completed their 6-month visit (54.2% information fraction), using a two-sided nominal significance level of 0.010 based on a Gamma (-3) alpha-spending function.</p> <p>The final 6-month analysis will be conducted when all randomized patients (3324) have performed their 6-month visit. The two-sided nominal significance level to be used at this final 6-month analysis is 0.046.</p> <p>Patients with missing HbA1c data at 6 months will be regarded as not having reached HbA1c target.</p>
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	<p>In order to examine the consistency of the primary analysis, the individual components of HbA1c target attainment and absence of any documented symptomatic (BG \leq 70 mg/dl) or severe hypoglycemia will also be evaluated. The proportion of patients without documented symptomatic (BG \leq 70 mg/dl) or severe hypoglycemia will be compared between treatment groups using logistic regression, adjusting for randomization strata and other baseline characteristics as clinically appropriate. The proportion of patients reaching individualized HbA1c target will be analyzed as for the composite primary endpoint.</p> <p>Further, a predictive subgroup identification method will be employed to identify subgroups of potential responders.</p> <p>Analysis of secondary endpoints</p> <p>Persistence:</p> <ul style="list-style-type: none"> • The incidence of patients completing the 6 month and the 12 month periods will be described by treatment arm, • The proportion of patients who withdraw at Month 6 and Month 12 will be analyzed by treatment group using a logistic regression methodology as described above, • Cumulative incidence of treatment discontinuation will be plots/estimates by treatment arm using a Kaplan-Meier (KM) by treatment arm, • Extent of exposure as well as treatment compliance will also be described by treatment arm. <p>In addition, for US patients, a medication possession ratio (MPR) will be assessed based on number of days that patients had possession of study drug based on prescription date and days of supply. A MPR of 80% would be indicative of patients being persistent on study medication.</p> <p>For patients from US and Canada where there is not data available for calculation of the MPR, the extent of study treatment exposure and compliance will be assessed and summarized by observance of the actual treatment received within the safety population.</p> <p>The duration of exposure during the study will be the total number of days of administration of IMP, accounting for temporary drug discontinuation.</p> <p>The duration of exposure to the open-label IMP during the study is defined as: (Date of the last IMP administration – date of the first IMP administration)+1.</p> <p>Efficacy Endpoints:</p> <p>The change in HbA1c from baseline to 6 months will be analyzed using a mixed-effect model with repeated measures (MMRM) approach under the missing at random framework, using an adequate contrast at Month 6. The model will include fixed categorical effects of treatment arm, visit, treatment-by-visit interaction, randomization strata: individualized HbA1c target (<8%/<7%), SU use ever (y/n), GLP-1 RA use ever (y/n), and baseline HbA1c (as continuous), as well as baseline HbA1c-by-visit interaction.</p> <p>The change in fasting plasma glucose and bodyweight from baseline to 6 and 12 months will be analyzed in a similar fashion to the change in HbA1c.</p>
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	<p>The proportion of patients with individualized HbA1c target attainment without hypoglycemia will be analyzed as described for the primary endpoint.</p> <p>PROs:</p> <p>Self-reported patient satisfaction and hypoglycemia (DTSQ and Hypoglycemia Patient Questionnaire): Satisfaction scores at 6 and 12 months will be compared between treatment groups using a MMRM approach as described for the continuous efficacy variables. To adjust for the baseline differences between treatment groups, logistic regression will be conducted, adjusting for randomization strata; individualized HbA1c target (<8%/<7%), SU use ever(y/n), GLP-1 RA use ever(y/n) and baseline HbA1c(as continuous).</p> <p>Global Effectiveness Scale (GES): At each study endpoint, the proportion of patients and providers who reported “Excellent” or “Good” at 6 and 12 months will be analyzed using logistic regression as described previously.</p> <p>Health resource utilization for each treatment group will be analyzed by descriptive analysis. Multivariate analysis will be used to evaluate the difference in health resource utilization and cost between treatment groups with adjustment for specific covariates.</p> <p>Safety Endpoints:</p> <p>The incidence of hypoglycemia will be analyzed using logistic regression, adjusting for randomization strata and other baseline characteristics as clinically appropriate and if the model permits.</p> <p>The rate per patient-year of hypoglycemic events will be analyzed using an over-dispersed Poisson regression model, adjusting for randomization strata and other baseline characteristics as clinically appropriate and if the model permits.</p>
DURATION OF STUDY PERIOD (per patient)	<p>The prospective phase of the trial will consist of:</p> <ul style="list-style-type: none"> • 1 week screening period at site, • 26 week (6 month) treatment period, • 26 week (6 month) extension period, • The maximum study duration will be 53 weeks per patient.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



R : Randomization

Cs and C180 : Clinical exam including vital signs: weight, height, systolic and diastolic blood pressure, heart rate as well as comprehensive physical exam

Ls: Hemoglobin A1c, fasting plasma glucose, serum creatinine, serum liver function tests including AST, ALT, total bilirubin, and alkaline phosphatase, serum pregnancy test for women of childbearing potential

L180: Hemoglobin A1c, fasting plasma glucose, serum pregnancy test for women of childbearing potential

L360: Hemoglobin A1c, fasting plasma glucose, serum pregnancy test for women of childbearing potential

Ps: DTSQ, Hypoglycemia Patient Questionnaire

P180 and P360: DTSQ, Hypoglycemia Patient Questionnaire, Patient GES, Provider GES

1.2 STUDY FLOW CHART

	Screening	Treatment Period				
VISIT	1	2			3	4
WEEK	-1	0			26±4	52±4
DAY	-7	1±7	45	90	180±30	360±30
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Patient Demography	X					
Medical/Surgical History	X					
Prior Medication History	X					
Physical Examination	X				X	X
Vital Signs (including body weight)	X				X	X
DTSQs	X	X			X	X
DTSQc						X
Hypoglycemia Patient Questionnaire	X	X			X	X
PAM	X					
Patient: Global Effectiveness Scale					X	X
Provider: Global Effectiveness Scale					X	X
Randomization		X				
IVRS call	X	X			X	X
Treatment:						
Dispensation of IMP		X				
Concomitant Medication	X	X			X	X
Compliance					X	X
Insulin Pen Instruction		X				
Blood glucose meter dispensing and training		X				
E-diary dispensing and training		X				
Offer to Enroll in PSP		X				
Insulin dose					X	X

	Screening	Treatment Period				
Safety:						
AE /SAE recording	X	X			X	X
Diary Reviews at visits		X			X	X
Hypoglycemia review of electronic source ^a			X	X		
Health Care Utilization		X			X	X
Laboratory Testing:						
Hemoglobin A1c	X				X	X
Fasting plasma glucose	X				X	X
Serum creatinine	X					
Serum LFTs (AST, ALT, total bilirubin, alkaline phosphatase)	X					
Pregnancy test (for women of childbearing potential) ^b	X				X	X

^a Approximately Day 45 and approximately Day 90, review of electronic source without on site or telephone visit

^b Pregnancy status should be checked by serum pregnancy testing prior to exposure to the investigational product, urine pregnancy tests may be done at subsequent visits

2 TABLE OF CONTENTS

1	FLOW CHARTS	11
1.1	GRAPHICAL STUDY DESIGN	11
1.2	STUDY FLOW CHART	12
2	TABLE OF CONTENTS	14
3	LIST OF ABBREVIATIONS	19
4	INTRODUCTION AND RATIONALE	20
5	STUDY OBJECTIVES	24
5.1	PRIMARY	24
5.2	SECONDARY OBJECTIVES	24
6	STUDY DESIGN	25
6.1	DESCRIPTION OF THE PROTOCOL	25
6.2	DURATION OF STUDY PARTICIPATION	25
6.2.1	Duration of study participation for each patient	25
6.2.2	Determination of end of clinical trial (all patients)	26
6.3	INTERIM ANALYSIS	26
6.4	STUDY COMMITTEES	26
6.4.1	Data Monitoring Committee	26
7	SELECTION OF PATIENTS	28
7.1	INCLUSION CRITERIA.....	28
7.2	EXCLUSION CRITERIA	28
7.2.1	Exclusion criteria related to study methodology	28
7.2.2	Exclusion criteria related to the active comparator and/or mandatory background therapies.....	29
7.2.3	Exclusion criteria related to the current knowledge of Sanofi compound	29
8	STUDY TREATMENTS	30
8.1	INVESTIGATIONAL MEDICINAL PRODUCT (IMP)	30
8.1.1	Name of the investigational medicinal product	30

8.1.2	Pharmaceutical forms of the investigational medicinal product and injection devices	30
8.1.3	The dose of the administered Toujeo and control drugs	31
8.1.4	Route and method of investigational medicinal product administration.....	31
8.1.5	Timing of investigational medicinal product	31
8.1.6	Starting dose of investigational medicinal product.....	31
8.1.7	Evaluation of patients not meeting glycemic goals	32
8.1.8	Reasons for treatment discontinuation	32
8.2	NONINVESTIGATIONAL MEDICINAL PRODUCTS (NIMP)	32
8.3	BLINDING PROCEDURES.....	33
8.4	METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP	33
8.5	PACKAGING AND LABELING	33
8.6	STORAGE CONDITIONS AND SHELF LIFE	34
8.7	RESPONSIBILITIES	34
8.8	TREATMENT ACCOUNTABILITY AND COMPLIANCE	35
8.9	CONCOMITANT MEDICATION.....	35
8.9.1	Prohibited medications.....	36
9	ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT	37
9.1	PRIMARY ENDPOINT	37
9.2	SECONDARY ENDPOINTS	37
9.2.1	Secondary efficacy endpoints	37
9.2.2	Other endpoint(s)	38
9.2.2.1	Observation period of efficacy variables	38
9.2.2.2	Efficacy assessment methods	38
9.2.3	Safety endpoints	39
9.2.3.1	Hypoglycemia classification	40
9.2.3.2	Adverse events, serious adverse events	41
9.2.3.3	Adverse event observation period	41
9.2.3.4	Death observation periods	42
9.2.3.5	Laboratory safety variables	42
9.2.3.6	Vital Signs	42
9.2.3.7	Electrocardiogram variables	42
9.2.3.8	Injection site reactions, hypersensitivity reactions and immunogenicity.....	42
9.3	OTHER ENDPOINTS	43
9.3.1	Patient reported outcomes.....	43
9.3.2	Health utilization endpoints	43

9.4	FUTURE USE OF SAMPLES	44
9.5	APPROPRIATENESS OF MEASUREMENTS	44
10	STUDY PROCEDURES	45
10.1	VISIT SCHEDULE.....	45
10.1.1	Screening Period.....	46
10.1.1.1	On-site Visit 1 (Week -1) Screening visit	46
10.1.1.2	Baseline Visit 2 (Week 0, Day1) +/-7 days	47
10.1.1.3	Visit 3 (Day 180) +/- 30 days	48
10.1.1.4	Visit 4 (Day 360) +/- 30 days	48
10.1.1.5	Unscheduled phone visits	49
10.1.1.6	Glucose review at Day 45 and Day 90	49
10.1.1.7	“Standard of Care” visits	49
10.2	DEFINITION OF SOURCE DATA.....	50
10.2.1	Source data to be found in patient’s file.....	50
10.2.1.1	Source data verification requirements for screen failures	50
10.3	HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION.....	51
10.3.1	Temporary treatment discontinuation with investigational medicinal product(s)	51
10.3.2	Permanent treatment discontinuation with investigational medicinal product(s)	51
10.3.3	List of criteria for permanent treatment discontinuation.....	51
10.3.4	Handling of patients after permanent treatment discontinuation	52
10.3.5	Procedure and consequence for patient withdrawal from study.....	52
10.4	OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING	53
10.4.1	Definitions of adverse events.....	53
10.4.1.1	Adverse event	53
10.4.1.2	Serious adverse event	53
10.4.1.3	Adverse event of special interest.....	54
10.4.2	Serious adverse events waived from expedited regulatory reporting to regulatory authorities.....	55
10.4.3	General guidelines for reporting adverse events	55
10.4.4	Instructions for reporting serious adverse events	56
10.4.5	Guidelines for reporting adverse events of special interest.....	56
10.4.6	Guidelines for management of specific laboratory abnormalities	56
10.5	OBLIGATIONS OF THE SPONSOR	57
10.6	SAFETY INSTRUCTIONS	58
10.6.1	Hypoglycemia.....	58
10.6.2	Local safety	59

10.6.3	Follow-up of laboratory abnormalities	59
10.6.4	SMPG.....	60
10.7	ADVERSE EVENTS MONITORING	60
11	STATISTICAL CONSIDERATIONS	61
11.1	DETERMINATION OF SAMPLE SIZE.....	61
11.2	DISPOSITION OF PATIENTS	61
11.3	ANALYSIS POPULATIONS	62
11.3.1	Efficacy populations	62
11.3.1.1	Intent-to-treat population	62
11.3.2	Safety population	62
11.4	STATISTICAL METHODS	62
11.4.1	Extent of study treatment exposure and compliance.....	62
11.4.1.1	Extent of investigational medicinal product exposure.....	62
11.4.2	Analyses of efficacy endpoints.....	62
11.4.2.1	Analysis of primary efficacy endpoint(s)	62
11.4.3	Analyses of safety data	64
11.4.4	Analyses of Patient Reported Outcomes.....	64
11.4.5	Health-related Quality of Life/health economics variables.....	65
11.5	INTERIM ANALYSIS.....	65
12	ETHICAL AND REGULATORY CONSIDERATIONS.....	66
12.1	ETHICAL AND REGULATORY STANDARDS	66
12.2	INFORMED CONSENT	66
12.3	INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)	67
13	STUDY MONITORING	68
13.1	RESPONSIBILITIES OF THE INVESTIGATOR(S).....	68
13.2	RESPONSIBILITIES OF THE SPONSOR.....	68
13.3	SOURCE DOCUMENT REQUIREMENTS.....	69
13.4	USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST	69
13.5	USE OF COMPUTERIZED SYSTEMS.....	69
14	ADDITIONAL REQUIREMENTS.....	70

14.1	CURRICULUM VITAE	70
14.2	RECORD RETENTION IN STUDY SITES	70
14.3	CONFIDENTIALITY	70
14.4	PROPERTY RIGHTS.....	71
14.5	DATA PROTECTION.....	71
14.6	INSURANCE COMPENSATION.....	71
14.7	SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES	72
14.8	PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE.....	72
14.8.1	By the Sponsor.....	72
14.8.2	By the Investigator	73
14.9	CLINICAL TRIAL RESULTS	73
14.10	PUBLICATIONS AND COMMUNICATIONS	73
15	CLINICAL TRIAL PROTOCOL AMENDMENTS	74
16	BIBLIOGRAPHIC REFERENCES.....	75
17	APPENDICES.....	77
	APPENDIX A PATIENT SUPPORT PROGRAM	78
	APPENDIX B GENERAL GUIDANCE FOR THE FOLLOW-UP OF LABORATORY ABNORMALITIES BY SANOFI.....	79
	APPENDIX C GLOBAL EVALUATION OF TREATMENT EFFECTIVENESS	83
	APPENDIX D DIABETES TREATMENT SATISFACTION QUESTIONNAIRE	84
	APPENDIX E DIABETES TREATMENT SATISFACTION QUESTIONNAIRE (CHANGE).....	85
	APPENDIX F INSIGNIA PATIENT ACTIVATION MEASURE	86
	APPENDIX G HEALTHCARE EFFECTIVENESS DATA AND INFORMATION SET (HEDIS) CRITERIA FOR INDIVIDUALIZED HBA1C TARGETS.....	88
	APPENDIX H HYPOGLYCEMIA PATIENT QUESTIONNAIRE.....	89

3 LIST OF ABBREVIATIONS

ADA:	American Diabetes Association
AE:	adverse event
AESI:	adverse event of special interest
BG:	blood glucose
CDE:	certified diabetes educator
CRF:	case report form
DTSQc:	diabetes treatment satisfaction questionnaire change version
DTSQs:	diabetes treatment satisfaction questionnaire status version
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
GES:	global effectiveness scale
GLP:	glucagon like peptide
GSO:	global safety officer
HbA1c:	glycosylated hemoglobin
HIPAA:	health insurance portability and accountability act
HLGT:	high group level term
HLT:	high level term
IMP:	investigational medicinal product
IVRS/IWRS:	interactive voice response system/interactive web response system
MedDRA:	Medical Dictionary for Regulatory Activities
MPR:	medication possession ratio
NIMP:	non-investigational medicinal product
OAD:	oral anti-diabetic agent
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PRO:	patient reported outcomes
PSP:	patient support program
PT:	preferred term
SMPG:	self-measured plasma glucose
SOC:	system organ class
T2DM:	type 2 diabetes

4 INTRODUCTION AND RATIONALE

Type 2 diabetes mellitus is a progressive disease characterized by relative insulin deficiency and eventual need for supplemental insulin therapy (1), (2). Appropriate initiation and titration of insulin therapy is essential to enhance adherence to therapy and reach glycemic targets (3). Attainment of these targets is associated with a reduction in the incidence of long term diabetes-related microvascular complications such as retinopathy, nephropathy, and neuropathy (4), (5).

Currently available basal insulins are effective but associated with undesirable adverse effects such as hypoglycemia and weight gain (3). Insulins currently in development seek to provide similar or improved efficacy with an improved safety profile. Toujeo (insulin glargine 300 units/ml) is a basal insulin currently submitted for FDA approval and potential launch in 2015. Toujeo has distinct pharmacokinetic (PK) and pharmacodynamic (PD) profiles compared to Lantus (insulin glargine 100 units/ml) which arise from its unique formulation (6), (7). The higher concentration of insulin in Toujeo allows a smaller volume to deliver the same number of glargine units as Lantus with a corresponding smaller surface area for the subcutaneous glargine depot which forms after injection. This smaller surface area results in a more gradual release of insulin glargine resulting in a flatter and smoother PK profile and longer duration of action on the PD profile (6), (7).

Toujeo has been shown to be non-inferior to Lantus with respect to glycosylated hemoglobin (HbA1c) reduction in phase 3 studies (the EDITION program) (8), (9), (10). Of note, a significantly lower percentage of patients with type 2 diabetes experienced confirmed or severe nocturnal hypoglycemic events on Toujeo compared to Lantus (8), (9), (10). This finding suggests that a safer initiation and titration of basal insulin may be possible with Toujeo compared to other currently available basal insulins especially when coupled with adequate patient support.

Although the EDITION studies provided efficacy and safety data required for regulatory review of Toujeo by the appropriate agencies, reimbursement for a new insulin by payers will require additional evidence establishing the value of Toujeo in real world clinical practice. The unique profile of Toujeo compared to Lantus and other basal insulins should allow target HbA1c achievement with a lower risk of hypoglycemia. This, in turn, should result in greater patient satisfaction with treatment. A greater number of patients at glycemic goal without hypoglycemia should also lead to decreased resource utilization and associated healthcare costs. This combination of improved clinical outcomes accompanied by greater patient satisfaction and decreased healthcare costs is of considerable interest to payers globally (11).

Real world study design is particularly relevant to payers as it is not constrained by the parameters required for traditional clinical trials which demonstrate benefit in a narrowly defined target population which may not be representative of the population that may benefit from treatment. Real world studies should mimic real world clinical practice by: minimizing the requirement for monitoring (typically possible only when treatment is approved and available) and limiting protocol mandated visits to only those needed for designated endpoints. Integrity of the “real world” nature should be preserved as much as possible since each compromise will decrease impact and relevance to payers. This also pertains to use of study specific treatment algorithms

and interventions and treatment should be according to the usual practice at the site. In addition, patients should be selected and identified through clinical practice sites and not through research sites as in clinical trials. Minimal study inclusion and exclusion criteria should be considered so as to include a broad patient profile for generalizability of results.

The proposed pragmatic trial design seeks to demonstrate the benefit of Toujeo with its associated patient support program in achieving individualized glycemic targets without hypoglycemia in uncontrolled insulin naïve patients with type 2 diabetes who are initiating basal insulin therapy in a clinical practice setting. The study is a randomized, controlled, open label parallel group real world study with few inclusion/exclusion criteria and conducted at clinical practice sites without study mandated titration algorithms.

The importance of diabetes education and patient self-management in the overall management of diabetes has been demonstrated with improvements in some clinical outcomes and also in measures of health care utilization. The best strategy needs to be determined in the real world setting for the support of patients who are insulin naïve and initiating insulin treatment. In this pragmatic study, a real world approach to providing patient education and support is incorporated via the patient support programs.

Achieve Control includes a planning phase and the prospective study phase. During the planning phase of the trial, payer, research organization, and HCP databases are reviewed to identify appropriate sites and patients eligible for the study. Patients may also be identified through review of these databases including at the site level on an ongoing basis during the trial. The inclusion/exclusion criteria will be applied to relevant databases to identify appropriate subjects, ensuring that at least 12 months of baseline medical data are available and patients had actively sought care at the site in the last 12 months. The intent of the study is to demonstrate the efficacy of Toujeo in a Real World setting where there is ongoing care provided by the site investigator prior to, during the trial, and after the trial is over.

In the prospective phase prospective and will begin after potential candidates are screened, and subsequently randomized to:

- 1) Toujeo with its available patient support program ([Appendix A](#)) or
- 2) Lantus ([12](#)) or Levemir ([13](#)) with or without a patient support program.

Randomization will be 1:1 between the two arms of the study and the choice of comparator basal insulin will be based on the usual practice at the clinical site and not by randomization.

The prospective phase will include an initial 6 month period for assessment of primary and secondary efficacy endpoints and safety endpoints followed by a 6 month extension period for evaluation of additional endpoints to include PRO and health care utilization endpoints at 1 year after randomization. It will also include an interim analysis (IA), for overwhelming efficacy on the primary endpoint, planned to be conducted when 1800 patients have been randomized and completed their 6-month visit. An independent Data Monitoring Committee (DMC) will review data from this IA.

The primary endpoint is defined as the proportion of patients with individualized HbA1c target attainment per Healthcare Effectiveness Data and Information Set (HEDIS) criteria (14) (provided in [Appendix G](#)) at 6 months without documented symptomatic ($BG \leq 70$ mg/dl) or severe hypoglycemia at any time of day from baseline to 6 months.

Based on data from the EDITION program (8), (9), (10) the expected difference in achievement of this endpoint for the two target HbA1c levels specified by HEDIS are as follows: 1) 5.5% difference in favor of Toujeo with target HbA1c $<7\%$, with a 30.1% rate in the Toujeo arm, and 2) 5.4% difference in favor of Toujeo with target HbA1c $<8\%$, with a 55.8% rate in the Toujeo arm. This difference was used in the calculation of the estimated sample size based on the assumption from commercially insured population databases that 70% of the study patients would have a target HbA1c $<7\%$ and 30% would have a target HbA1c $<8\%$ (15).

The proposed study also intends to collect data on several secondary endpoints. These include:

1. Change in HbA1c from baseline to 6 months and 12 months;
2. Persistence/discontinuation of basal insulin therapy;
3. Patient reported outcomes of treatment satisfaction and experience of hypoglycemia;
4. Health resource utilization and cost and;
5. Hypoglycemia.

Persistence/Discontinuation of basal insulin therapy:

Discontinuation from basal insulin therapy will be defined as a patient not being persistent with their therapy. In the US, reimbursement vouchers will be used to evaluate discontinuation at 6 and 12 months for patients enrolled in the study. Additionally, a medication possession ratio (MPR) will be assessed based on number of days that patients had possession of study drug based on prescription date and days of supply. A medication possession ratio (MPR) of 80% would be indicative of patients being persistent on study medication (16).

Patient-Reported Outcomes (PRO):

Patients will complete self-reported questionnaires at designated time points in the study:

The Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs) (17) will be used to evaluate patient satisfaction with treatment and patient perception of blood glucose control over a several week period. The DTSQs is comprised of 8 questions which are answered on a Likert scale from 0 to 6. Responses to these questions would be summarized into the three domain scores GES of Total Treatment Satisfaction, Hyperglycemia Perception and Hypoglycemia Perception such that a higher score would be indicative of better satisfaction..

The Diabetes Treatment Satisfaction Questionnaire Change Version (DTSQc) will be used to measure change in treatment satisfaction at 12 months.

Patients will also complete the Hypoglycemia Patient Questionnaire (18) which will require them to report frequency of hypoglycemia experienced during the course of the study. Proportion of patients reporting moderate or severe hypoglycemia will be compared between treatment groups.

Patient and Physician reported Global Effectiveness Scale (GES): The measure, originally developed to assess the impact of treatment on asthma control, will be adapted for diabetes.

Health Resource Utilization

The proposed study also intends to collect data on health resource utilization from payer patients who agree to release their claims data which will include physician office visits, emergency room (ER) visits and hospitalizations and health care costs. Data for these endpoints will be obtained from the health claims database of the payer involved in the study. Occurrence of the events will be summarized over 6 and 12 month time periods for each patient to confirm presence of the events at the corresponding time points.

Health resource utilization information will be collected through the supplemental case report form (CRF) at each site for all patients in US and Canada, whether they have claims data or not. Health care costs will not be collected from non-payer sites.

5 STUDY OBJECTIVES

5.1 PRIMARY

- Demonstrate clinical benefit of Toujeo in achieving individualized HEDIS HbA1c targets (<8% if age \geq 65 years or with defined comorbidities (as listed [Appendix G](#) or otherwise <7%) at 6 months without documented symptomatic ($BG \leq 70$ mg/dl) or severe hypoglycemia at any time of day from baseline to 6 months in uncontrolled insulin naive patients with type 2 diabetes initiating basal insulin therapy in a real world setting.

5.2 SECONDARY OBJECTIVES

Secondary objectives are to compare Toujeo to other commercially available basal insulins at 6 and 12 months after initiating insulin therapy in a real world setting in terms of:

- Patient persistence with assigned basal insulin therapy.
- Risk of hypoglycemia including the incidence and rate of documented symptomatic and severe hypoglycemia.
- Changes in HbA1c, fasting plasma glucose (FPG), body weight.
- Differences in patient and provider reported outcomes (including Diabetes Treatment Satisfaction Questionnaire Status and Change Versions [DTSQs and DTSQc]), Hypoglycemia Patient Questionnaire, and patient and provider reported Global Effectiveness Scale (GES).
- Healthcare resource utilization including hospitalizations and emergency department or other provider visits and healthcare costs.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a multi-center open label randomized active controlled 2 arm parallel group comparative “real world” or “pragmatic” trial in patients with type 2 diabetes who are insulin naïve and uncontrolled on two or more diabetes medications including oral anti-diabetic agents (OADs) and/or GLP-1 RA. Patients are randomized 1:1 to Toujeo or “Standard of Care” insulin without further sub randomization and with use of the SOC insulin determined by preference of site investigator and practice patterns of the site.

The goal of the study is to demonstrate that Toujeo with its available patient support program will be superior to other commercially available basal insulin, specifically Lantus and Levemir with a patient support program recommended by the site in attainment of individualized HEDIS HbA1c targets at 6 months without documented symptomatic ($BG \leq 70$ mg/dl) or severe hypoglycemia at any time of day from baseline to 6 months.

The protocol allows for nearly all OADs and GLP-1 RA for daily use as background medication as allowed for use with insulin in the label.

Stratification factors for randomization include GLP-1 RA use ever (y/n), SU use ever (y/n) and HbA1c ($<9\%$ / $\geq 9\%$).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

During the planning phase of the trial, payer, research organization, and provider data bases will be reviewed to identify sites and patients eligible for the study.

After the data base review, the trial will consist of:

- 1 week screening period at site by clinician to screen the identified potential subjects
- 26 week treatment period for primary efficacy endpoint
- 26 week extension period for collecting persistence data and additional safety data.

The maximum study duration will be 53 weeks per patient.

For patients who prematurely discontinue the trial, the end of treatment visit assessments (Day 180 data) will be performed at the time of discontinuation at an EOT visit. In addition, an early end of trial (EOT) CRF page will be completed which includes the reason for stopping the treatment. Patients are then asked to return for their regularly schedule visits off treatment.

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial is reached as soon as last patient visit is performed.

6.3 INTERIM ANALYSIS

One formal IA is planned for the purpose of overwhelming efficacy of primary endpoint when 1800 patients have been randomized and completed their 6 month visit (Day 180). Statistical operating characteristics of this analysis, including the α -spending function to control the Type I error, are described in the statistical considerations (see [Section 11.5](#)).

Limited efficacy data is available regarding the initiation of insulin treatment in a “Real World” or pragmatic study. Achieve Control is a study designed to provide data on the efficacy and safety of Toujeo in a “Real World” setting. The unique primary composite endpoint has clinical relevance for managed care organizations and the study will provide safety and efficacy data for health care providers in their usual practice setting, rather than a traditional RCT.

The unanticipated challenges of recruiting patients in this unique trial design have resulted in delayed enrollment. Based on the need for real life Toujeo data for informing the decision makers on insulin use in managed care organizations, the objective of the study and IA is to generate real world evidence for the purpose of healthcare reimbursement and scientific communication only.

Results of this IA will be reviewed by the DMC ([Section 6.4.1](#)). The DMC procedures will be done with the utmost possible care for protecting clinical data integrity and for maintaining the blinding of Sponsor representatives and trial team so as not to impact final interpretation of the study results.

6.4 STUDY COMMITTEES

6.4.1 Data Monitoring Committee

An independent DMC will be in charge of reviewing the unblinded efficacy results of the interim analysis. The DMC will give appropriate recommendations to the Sponsor on whether overwhelming efficacy is reached or not for the primary composite endpoint. The DMC may make recommendations regarding any measures that may be required for ensuring the integrity of the study results during the execution of its primary mission including assessing the risk benefit.

Overwhelming efficacy will be shown if the p-value of the superiority test for comparison of Toujeo and comparator basal insulins on the primary endpoint is below 0.010 with a higher proportion of patients reaching the primary endpoint in the Toujeo group.

The corresponding power to show overwhelming efficacy at interim analysis under the alternative hypothesis is of 45%.

If overwhelming efficacy is not shown (probability of 55% under the alternative hypothesis) the Sponsor would not see the unblinded data, and no results would be communicated. If

overwhelming efficacy is shown (probability of 45% under the alternative hypothesis) the Sponsor would see the data, and results would be communicated in agreement with the DMC. It could be considered to stop the recruitment (total sample size at that time estimated to be between 2600-3000 patients). However, study participation for patients already recruited would continue as planned. In either case (superiority achieved at interim or not), the study will continue up to month 6 and up to month 12 as planned, with analyses performed on whole study population.

The DMC consists of 3 members 2 of whom are clinicians with expertise in diabetology and one biostatistician. Members of the DMC are independent of those performing these studies, being neither Investigators nor employees of the Sponsor and without conflict of interest regarding study outcomes. For details, please refer to the DMC charter.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

- I 01. Patients with type 2 diabetes (T2DM), as defined by the ADA/WHO, diagnosed for at least 1 year at the time of the screening visit, insufficiently controlled after at least 1 year of treatment with 2 or more of the following: oral agents (metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, or SGLT-2 inhibitors) or GLP-1 receptor agonists for daily use and approved for use with insulin (Victoza[®], Byetta[®], Adlyxin[®]).
- I 02. Adult patients who have signed an Informed Consent Form and Health Insurance Portability and Accountability Act (HIPAA) Authorization Form

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in [Section 7.1](#) will be screened for the following exclusion criteria which are sorted and numbered in the following 4 subsections:

7.2.1 Exclusion criteria related to study methodology

- E 01. HbA1c <8.0% or >11.0%.
- E 02. Males or females <18 years of age.
- E 03. Type 1 diabetes mellitus
- E 04. Any clinically significant abnormality identified on physical examination, laboratory tests, or vital signs at the time of screening, or any major systemic disease resulting in short life expectancy that in the opinion of the Investigator would restrict or limit the patient's successful participation for the duration of the study.
- E 05. Use of any product containing insulin (Lantus, Levemir, Humulin, Novolin, Humalog, Novolog, Apidra, Afrezza, Toujeo, Tresiba) since the time of diagnosis with T2DM prior to screening other than temporary use such as during a pregnancy or hospitalization or other short term outpatient use (\leq 10 days) during an acute medical event.
- E 06. Use of oral hypoglycemic agents other than those noted in the inclusion criteria; GLP-1 receptor agonists for weekly use (Trulicity[®], Tanzeum[®], Bydureon[®]) or not approved for use with insulin or any investigational agent (drug, biologic, device) within 3 months prior to the time of screening.
- E 07. All contraindications to commercially available insulin therapy or warnings/precautions of use as displayed in the respective national product labeling for these products.

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

- E 08. All contraindications of the positive control/calibrator/protocol-mandated background therapy(ies) or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling that was used for defining these exclusion criteria.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

- E 09. Pregnant or breastfeeding woman.
- E 10. Woman of childbearing potential not protected by highly-effective method(s) of birth control (as defined in a local protocol amendment in case of specific local requirement) and/or who are unwilling or unable to be tested for pregnancy.

8 STUDY TREATMENTS

Diet and lifestyle counseling is an essential component of this trial. Patients in the trial will have ongoing diet and lifestyle counseling provided at their clinical practice site by the clinician or staff as per their usual custom. Patients may also be enrolled in diabetes education programs at the discretion of the investigator. At the time of randomization, the patients randomized to Toujeo will be offered the additional support through an available patient support program (PSP) unique for Toujeo. This will include an initial detailed session by a professional competent in treating type 2 diabetes mellitus. Patients randomized to the “standard of care” arm of the trial will be offered a support program that may be office based, hospital affiliated, community based or provided by a payer.

Investigators and site staff will provide educational materials and training both oral and written consistent with the local standard of care to ensure their patients understand the importance of routine monitoring and dose adjustment of their basal insulin. The goal for all patients must be to attain good glycemic control by treating to a defined glucose target without an increase in hypoglycemia. This should be done consistent with the “real world setting”.

8.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

8.1.1 Name of the investigational medicinal product

Sanofi’s Toujeo HOE/901 U300 glargine is the tested drug and U100 insulin glargine (Lantus) and insulin detemir (Levemir) are the comparator/control drugs.

8.1.2 Pharmaceutical forms of the investigational medicinal product and injection devices

Handling procedures of the pen and needles and administration technique is provided; see package insert for Toujeo SoloSTAR pen and Sanofi sponsored materials for Lantus U100 SoloSTAR[™] pen and Novo sponsored materials for the Levemir[®] FlexTouch[™].

Patients will be trained by the staff at the practice site, or by a certified diabetes educator (CDE) on the use of the injection devices as close as is possible to time of the randomization visit. A training pen may be requested by the site. Training may be performed with the initial pen to be used for administration of insulin after obtained from pharmacy in the US or with a training pen. Canadian sites may use one of the pens dispensed by the site.

The disposable pen injector allows for dose setting in the range of 1-80 U with minimum dose increments of 1.0 U.

If a pen-related event occurs, a PTC form should be completed if appropriate.

8.1.3 The dose of the administered Toujeo and control drugs

The dose of the administered basal insulin either Toujeo or the control drugs Lantus and Levemir depends on the self-measured plasma glucose (SMPG) data and occurrence of hypoglycemia and is at the discretion of the Investigator according to their usual practice in the real world setting. There is no recommended titration algorithm. Initial dose of basal insulin is to be consistent with the label.

8.1.4 Route and method of investigational medicinal product administration

Toujeo or the control drugs Lantus and Levemir are self-administered by deep subcutaneous injection, in the abdomen, thigh, arm or buttock and rotated within that area. Area and sites of injection will not be collected as data.

US:

Patients randomized to Toujeo will be prescribed the appropriate number of disposable Toujeo SoloSTAR disposable pens to be dispensed at their pharmacy. Patients randomized to Lantus or Levemir will be prescribed the appropriate number of pens to be dispensed at their pharmacy.

Canada:

The appropriate number of disposable pens for Toujeo or the control drugs Lantus and Levemir will be dispensed at the site. Insulin will be obtained from a commercial source and will be labeled according to local regulation for use in the study. Insulin will be dispensed by the site at investigator discretion and is not related to a visit. Specifically, there are no dispensing visits and no schedule for dispensing.

8.1.5 Timing of investigational medicinal product

Toujeo is self-administered by deep subcutaneous injection once daily in the morning or evening, not related to food intake, consistent with the label. Lantus is self-administered once daily in the morning or evening, also not related to food intake. Levemir is self-administered either once or twice daily, in the morning or evening.

8.1.6 Starting dose of investigational medicinal product

The starting dose for the insulin either tested or control will be consistent with the label and recorded in the source document.

The recommended target range for fasting, pre-prandial plasma glucose is 80 to 130 mg/dL (4.4 to 7.2 mmol/L), consistent with ADA guidelines. The dose of basal insulin will be adjusted to achieve this target. However, glycemic targets may be adapted for individual patients, if deemed necessary, eg, due to age, comorbid conditions, and individual patient considerations. The individual target range for glucose will be recorded in source documents. Insulin doses may be reduced or modified at any time for hypoglycemia.

Patients are to take their basal insulin once daily and with SMPG done per “usual habit” per provider instruction to assist in titration

8.1.7 Evaluation of patients not meeting glycemic goals

There are no central laboratory alerts on fasting plasma glucose or HbA1c to ensure that glycemic parameters remain below predefined threshold values. Patient SMPG monitoring is decided upon by site and patient diaries are reviewed at the time of visits to assist in titration. In addition, sites have access electronically to the information collected in the web based portal regarding hypoglycemia. In case SMPG are not improving as expected in spite of successive Investigational Medicinal Product (IMP) dose titration, the investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Compliance to treatment is appropriate
- There is no inter-current disease which may jeopardize glycemic control
- Compliance to diet and lifestyle is appropriate and per the usual custom for the site
- Regular blood glucose monitoring is being done since it is important to achieve blood glucose targets

Patients who are unable to achieve their target may have other medications “rescue medications” added to their existing regimen which might include the use of bolus or rapid acting insulin. When a medication is added or changed, the reason is captured in the e-CRF as well as the medication.

Patients who change their background medication for reason other than being unable to achieve their target are not considered using “rescue medication”.

8.1.8 Reasons for treatment discontinuation

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time. List of criteria for discontinuation are found in [Section 10.3.3](#) Handling of patients after discontinuation is described in [Section 10.3.4](#). Sites are to follow their local SOP for stopping treatment if there is a potential adverse event (AE) related to use of the IMP and according to investigator discretion.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS (NIMP)

Non-investigational products (NIMP) such as oral anti-diabetic agents and GLP-1 agonists for daily use and which can be used with insulin may be used throughout the trial. These agents may be changed or have their dose modified as part of the overall treatment plan during the trial. After randomization, any change in antidiabetic regimen including insulin dose and type will be done according to the local SOC.

8.3 BLINDING PROCEDURES

Toujeo SoloSTAR pen and the control drugs, Lantus SoloSTAR and Levemir FlexTouch are distinguishable and so this study is an open-label design. Despite the open label administration of the study insulin, the assessments of outcome, the HbA1c and FPG are determined in central laboratories blinded to the treatment received. The study team will review the data for the primary efficacy parameters and adverse events without treatment assignments.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

At the screening visit the investigator or designee calls the interactive voice response system/interactive web response system (IVRS/IWRS) for allocation of the patient number. The patient identification (patient number) is composed of 9-digit number containing the 3-digit country code, the 3-digit center code and the 3-digit patient chronological number (which is 001 for the first patient screened in a center, 002 for the second patient screened in the same center etc).

On V2 (Day 1), the investigator or designee contacts the IVRS/IWRS and provides the patient number provided by IVRS/IWRS at screening visit, date of birth, HbA1c, etc. Afterwards the IVRS/IWRS is called again each time for each new visit and but does not include “standard of care” visits, which are not considered trial visits (please see [Section 1.2](#)).

Treatment kits are not dispensed in US or Canada. In the US, the drugs are provided through pharmacy. The investigator provides the patient with a prescription for the insulin and a card to provide to the pharmacy to obtain the insulin, a “smart card” as a method of reimbursement. In Canada, IMP will be bought on local market and distributed through the sites not related to a visit and not recorded in IWRX.

Randomization will be performed centrally by IVRS/IWRS, and will be stratified by individualized HbA1c target (<8% / <7%), GLP-1 RA use ever (y/n), SU use ever (y/n) and HbA1c (<9% ≥9%). A patient cannot be randomized more than once in the study. Patients who need to be moved to another site will have a new randomization number assigned at the new site.

Patient may be rescreened if there is reason to believe there laboratory data will differ at the time of rescreening or if the patient misses the window for randomization. These patients are reviewed by Sponsor and approved on case by case basis.

8.5 PACKAGING AND LABELING

In the US, Toujeo and the comparator insulins are being dispensed via a standard dispensing pharmacy. The content of the labeling is in accordance with the local regulatory specifications and requirements. Toujeo will be provided as commercially available disposable Toujeo SoloSTAR pens. Lantus will be supplied as commercially available disposable Lantus SoloSTAR pens and Levemir as commercially available Levemir FlexTouch. There will be no special labeling or re-packaging for the trial and there will be no study specific label or study specific box. In Canada, Toujeo and the comparator insulins will be bought on local market and distributed

through the sites. The content of the labeling will be in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Patients in the US are responsible for the correct storage of “not in use” and “in-use” pens of investigational medicinal products Toujeo, Lantus, or Levemir. In Canada, sites are responsible for “not in use” pens and patients are responsible for “in use” pens.

Information on in-use stability and instructions for handling will be reinforced to the patient by the dispensing pharmacy and the site staff.

8.7 RESPONSIBILITIES

US:

The Investigator, the hospital pharmacist, or other clinic staff personnel are not allowed to store and dispense the IMP and are not be responsible for ensuring that the IMP used in the clinical trial is securely maintained. This is the responsibility of the patient.

All IMP will be prescribed by the Investigators to be dispensed at a pharmacy.

Patients are responsible for returning unused pens to site.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the prescribing pharmacy by the patient.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the dispensing pharmacy and smart card vendor will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Canada:

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP and NIMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator’s prescription and it is the Investigator’s responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party and allow the IMP or NIMP to be used other than as directed by this clinical trial protocol or dispose of IMP or NIMP in any other manner.

IMP is not dispensed using the IVRS/IWRS system; the correct allocation of IMP at each dispensation is collected in source data.

At each visit to dispense IMP after baseline as well as at the end of the treatment period, participants will take used and unused pens with them to the site.

8.8 TREATMENT ACCOUNTABILITY AND COMPLIANCE

US:

Medication use will be assessed by means of MPR and persistence measures based on data collected by the Smart card vendor (date of fill or refill and quantity of medication dispensed for 30 day supply). The site does not complete a treatment log form and no compliance information is entered into the e-CRF.

Canada:

An adequate supply of pre-packaged and labeled commercial insulin labeled for the study according to local regulations (IMP) with shelf life adequate to at least reach the next in-person visit will be provided starting with V2 (Day1, baseline).

The Investigator or delegate fills the Center IMP tracking log and inventory form per patient based on the used/unused IMP (study drug disposable pens) each time the patient receives the study drug.

8.9 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient at the same time as the IMP treatment.

- Therapy with short acting insulin either such as may occur during an acute illness or surgery or as a rescue medication is allowed.

8.9.1 Prohibited medications

Prohibited concomitant medication is limited to drugs contraindicated with use of basal insulin as per drug labels.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

All biological efficacy (HbA1c and FPG) and safety analysis will be performed by a Central Laboratory. Detailed information on samples drawing, management, and analysis will be provided in a specific manual.

9.1 PRIMARY ENDPOINT

- Proportion of patients with individualized HbA1c target attainment per HEDIS criteria <8% if age ≥ 65 years or with defined co-morbidities as listed in [Appendix G](#) or otherwise <7%) at 6 months without documented symptomatic (BG ≤ 70 mg/dl) or severe hypoglycemia at any time of day from baseline to 6 months.
- The individual components of individualized HbA1c target attainment and absence of any documented symptomatic (BG ≤ 70 mg/dl) or severe hypoglycemia will also be evaluated as supportive analyses to evaluate consistency.

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

- Change in HbA1c from baseline (obtained at screening visit within one week of study initiation) to 6 months.
- Proportion of patients who remain on assigned basal insulin therapy (persistent with assigned therapy) at 6 and 12 months.
- Proportion of patients with individualized HbA1c target attainment per HEDIS criteria at 6 months without documented symptomatic (BG < 54 mg/dl) or severe hypoglycemia at any time of day from baseline to 6 months.
- Proportion of patients with individualized HbA1c target attainment per HEDIS criteria at 12 months without documented symptomatic (BG < 54 mg/dl) or severe hypoglycemia at any time of day from baseline to 12 months.
- Proportion of patients with individualized HbA1c target attainment (per HEDIS criteria) at 12 months without documented symptomatic (BG ≤ 70 mg/dl) or severe hypoglycemia at any time of day from baseline to 12 months.

All secondary endpoints will be exploratory and descriptive and therefore no adjustments for multiplicity are specified.

9.2.2 Other endpoint(s)

- Change in HbA1c from baseline to 12 months,
- Change in fasting plasma glucose from baseline to 6 months and 12 months,
- Change in body weight from baseline to 6 months and 12 months,
- Basal insulin dose at 6 and 12 months.

9.2.2.1 Observation period of efficacy variables

- The efficacy whole study period is defined as the time from randomization up to Day 360 (Visit 4) and the extension to allow for collection of additional endpoint data such as health care utilization
- The efficacy 6-month period is defined as the time from randomization up to Day 180 (Visit 3)

9.2.2.2 Efficacy assessment methods

9.2.2.2.1 HbA1c measurement

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified Level I “National Glycohemoglobin Standardization Program” central laboratory at time points referenced according to the Flow Chart in [Section 1.2](#).

9.2.2.2.2 Fasting plasma glucose

Blood samples for FPG measurement are taken and measured at central laboratory at time points referenced according to the Flow Chart in [Section 1.2](#).

9.2.2.2.3 Self-measured plasma glucose during symptomatic hypoglycemia

At V2, the randomization visit, the Investigator or a member of the clinical staff will provide patients with a Bluetooth enabled blood glucometer including the corresponding supplies (lancets, control solutions, test strips etc) and training. Blood glucose values will be measured by the patient using the sponsor-provided blood glucometer throughout the trial after randomization. The patients will be instructed to bring the blood glucometers provided by the sponsor with them to each scheduled trial office visit and encouraged to also bring the meter to any SOC visits so the site can document proper meter function and facilitate hypoglycemia reporting. The blood glucometers should be calibrated according to instructions given in the package leaflet and the investigational site should also check regularly the glucometers using the provided control solutions for data validity.

At V2, the randomization visit, the Investigator or a member of the clinical staff will also provide the patient with an electronic diary and instruction on its use. Patients will be instructed to complete a hypoglycemia page in the e-diary for each hypoglycemic event. The site reviews hypoglycemia values and related clinical information before entering into the hypoglycemia pages

of the e-CRF at the visits. Whenever the patients feel hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible. Patients should be instructed to measure plasma glucose levels prior to the administration of glucose or carbohydrate intake whenever symptomatic hypoglycemia is suspected unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation. Patients are instructed on use of the paper back up form for hypoglycemia reporting for events recorded on non-sponsor meter or when the LBGE was not completed in the e-diary. In addition to review of hypoglycemia at the on-site visits, the sites will review hypoglycemia events electronically at approximately Day 45 and approximately Day 90 using information in the web based portal obtained from the electronic diary.

9.2.2.2.4 *SMPG done per usual habit*

SMPG done according to usual daily habit is not considered an efficacy endpoint but is reviewed by the clinical site to assist in titration oversight. This is done according to local, usual standard of care for the site and at the discretion of the Investigator who evaluates the individual patient's needs. This may be recorded in a paper diary provided by the site or patient according to usual practice or in the e-diary.

9.2.3 Safety endpoints

The following safety parameters will be analyzed in the clinical study report:

- Hypoglycemia (according to ADA Workgroup on Hypoglycemia),
- Adverse events, serious adverse events,
- Injection site reactions,
- Hypersensitivity reactions,
- Vital signs.

Hypoglycemia endpoints will be classified in categories ([Section 9.2.3.1](#)) after events have been characterized using ADA Working group.

- Incidence of documented symptomatic ($BG \leq 70$ mg/dl) nocturnal (0000-0559) hypoglycemia from baseline to 6 and 12 months, and 24-hour hypoglycemia from baseline to 12 months
- Rate of documented symptomatic ($BG \leq 70$ mg/dl) hypoglycemia (24 hour and nocturnal) from baseline to 6 and 12 months
- Incidence and rate of documented symptomatic ($BG < 54$) hypoglycemia (24 hour and nocturnal) from baseline to 6 and 12 months
- Incidence and rate of severe hypoglycemia (24 hour, per ADA definition) from baseline to 6 and 12 months

The observation period of safety data is divided into 3 main categories:

- The pre-treatment period is defined as the time from informed consent up to the time of the first injection of IMP
- The on-treatment period of the whole study is defined as the time from the first injection of IMP up to 1 day after the last injection of IMP
- The 6-month on-treatment period is defined as the time from first injection of IMP up to Week 26 (Visit 8) or up to 1 day after the last injection of IMP whichever comes earlier
- The post-treatment period is defined as the time starting 1 day after last injection of IMP (after the on-treatment period)

9.2.3.1 *Hypoglycemia classification*

Hypoglycemia events will be categorized as follows:

- **Severe hypoglycemia:** Severe hypoglycemia is an event requiring 3rd party assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that “requires 3rd party assistance” means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a “requires assistance” incident.
- **Severe hypoglycemia** will be qualified as an SAE only if it fulfills SAE criteria. All events of seizure, unconsciousness or coma must be reported as SAEs.
- **Documented symptomatic hypoglycemia:** Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L). Clinical symptoms that are considered to result from a hypoglycemic episode are, eg, increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, or coma.
- **Asymptomatic hypoglycemia:** Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L).
- **Probable symptomatic hypoglycemia:** Probable symptomatic hypoglycemia is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L); symptoms treated with oral carbohydrate without a test of plasma glucose.

- **Relative hypoglycemia:** (recently termed “pseudo-hypoglycemia”) is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration greater than 70 mg/dL (3.9 mmol/L).

Hypoglycemia events will be evaluated regardless the time of onset and in addition in the following time periods defined by time of the day:

- **Nocturnal hypoglycemia defined by time of the day:** any hypoglycemia of the above categories that occurs between 00:00 and 05:59 AM hours, regardless whether patient was awake or woke up because of the event.
- **Nocturnal hypoglycemia defined by sleep status:** any hypoglycemia of the above categories that occurs while the patient was asleep between bedtime and before getting up in the morning, ie, before the morning determination of fasting pre-breakfast SMPG and before any morning insulin injection and patient woke-up due to the hypoglycemia.
- **Daytime hypoglycemia:** any hypoglycemia of the above categories that occurs between 6:00 AM to 23:59.

Documented hypoglycemia will be analyzed in addition to the threshold of plasma glucose of less than or equal to 70 mg/dL (3.9 mmol/L), by using a threshold of plasma glucose of <54 mg/dL (3.0 mmol/L).

Hypoglycemic events will be transferred from the glucometer to a web based portal that serves as an electronic source document.

9.2.3.2 Adverse events, serious adverse events

All AEs and SAEs will be coded to a “Lower Level Term (LLT)”, “Preferred Term (PT)”, “High Level term (HLT)”, “High Level Group Term (HLGT)” and associated primary “System Organ Class (SOC)” using the version of MedDRA (Medical Dictionary for Regulatory Activities) currently in effect at the sponsor at the time of database lock. MedDRA terms for hypersensitivity and injection site reactions will be included. The occurrence of AEs and SAEs is recorded from the time of signed informed consent until the end of the study.

9.2.3.3 Adverse event observation period

All reported AEs and SAEs are collected from the time of signed informed consent until the end of the study (defined as patient’s last visit planned per protocol or the resolution/stabilization of all SAE and adverse events of special interest (AESIs). All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

If an AE/SAE is ongoing and not resolved by the end of the study observation period and leads to subsequent death of the patient, it will be reported.

The AE observations will be classified per the observation periods of safety data as defined above into:

- **Pre-treatment AEs** are AEs that developed or worsened or became serious during the pretreatment period.
- **Treatment-emergent AEs (TEAEs)** are AEs that developed or worsened or became serious during the on-treatment period.
- **Post-treatment AEs** are AEs that developed or worsened or became serious during the post-treatment period.

9.2.3.4 Death observation periods

The death observations are per the observation periods defined above. In addition, after the post-treatment period, death related to IMP as well as death resulting from TEAE must be reported to the Sponsor.

- Death on-study: deaths occurring during the on-study observation period (defined as the time from the signed informed consent date up to the end of the study, ie, last protocol planned visit or the resolution/stabilization of all SAE),
- Death on-treatment: deaths occurring during the on-treatment period.

9.2.3.5 Laboratory safety variables

The clinical laboratory data consist of blood analysis done at Central Laboratory at screening only (including LFTs and creatinine) Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables. No listings will be provided during the study and laboratory data from local laboratory related to AEs will not be entered into data base.

9.2.3.6 Vital Signs

Vital signs include heart rate and systolic and diastolic blood pressure in sitting position.

9.2.3.7 Electrocardiogram variables

ECG is not done routinely in the protocol. It may be done at the discretion of the investigator when clinically indicated. This data is not routinely recorded in the e-CRF and if abnormal, should be recorded as an AE.

9.2.3.8 Injection site reactions, hypersensitivity reactions and immunogenicity

No immunogenicity assessment is planned as part of the protocol. Injection site and local reactions are recorded on a standard AE page with its complementary page.

9.3 OTHER ENDPOINTS

9.3.1 Patient reported outcomes

Patients will complete self-reported questionnaires at designated time points in the study:

The Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs) will be used to evaluate patient satisfaction with treatment and patient perception of blood glucose control over a several week period. The DTSQs is comprised of 8 questions which are answered on a Likert scale from 0 to 6. Responses to these questions would be summarized into the three domain scores of Total Treatment Satisfaction, Hyperglycemia Perception and Hypoglycemia Perception such that a higher score would be indicative of better satisfaction. Mean differences in scores between groups would be evaluated to understand the impact of treatment on patient satisfaction.

The Diabetes Treatment Satisfaction Questionnaire Change Version (DTSQc) will be used to measure change in treatment satisfaction at 12 months. Scores for DTSQc treatment satisfaction items range from -3 to +3, and the sum of the treatment satisfaction scores range from -18 to +18. Positive scores are indicative of increases in treatment satisfaction relative to baseline measures. Perceived hyperglycemia and hypoglycemia items have scores that range from -3 to +3 in the DTSQc, with higher scores indicating more frequent perceived hyperglycemia or hypoglycemia by the end of the study. To control for baseline scores, DTSQs will be used as a measure of treatment satisfaction at baseline.

Patients will also complete the Hypoglycemia Patient Questionnaire which will require them to report frequency of hypoglycemia experienced during the course of the study. Responses to questions 5 & 6 on the Hypoglycemia Patient Questionnaire will be used to assess the endpoint. A patient report of 1 or more episodes of either moderate or severe hypoglycemia since the last visit will be indicative of patient experience of hypoglycemia. The proportion of patients reporting 1 or more episodes of either moderate or severe hypoglycemia will be compared between treatment groups.

Patient and Physician reported Global Effectiveness Scale (GES): This measure, originally developed to assess the impact of treatment on asthma control, will be adapted for diabetes (GES). The GES assesses impact of treatment on a 5-point scale (excellent, good, moderate, poor, or worsening of condition). These assessments will be completed twice by patients at 6 and 12 months. Physicians will complete the GES twice for each patient they manage at 6 and 12 months. Proportion of patients reporting “excellent” or “good” on the GES will be compared between the two treatment groups at each of the time points.

9.3.2 Health utilization endpoints

- Mean number and proportion of patients with hospitalizations over a 6 month and 12 month period,
- Mean number and proportion of patients with emergency room visits over a 6 month and 12 month period,

- Mean number of provider office visits and proportion of patients with specialty visits over a 6 month and 12 month period
- Mean overall and diabetes-related costs at 6 months and 12 months.

9.4 FUTURE USE OF SAMPLES

Not applicable.

9.5 APPROPRIATENESS OF MEASUREMENTS

The primary efficacy analysis will test superiority of Toujeo compared to other commercially available insulin in achieving individualized HEDIS HbA1c targets at 6 months without documented symptomatic or severe hypoglycemia as the primary endpoint. The 180 day duration of study treatment is considered to be sufficient for achieving steady state conditions with the commercially available basal insulins after randomization since there is no switching of basal, enabling an adequate assessment of time-dependent changes in HbA1c and the concomitant risk of hypoglycemia.

HbA1c is accepted by regulatory agencies as primary endpoint to support a claim based on glycemic control.

HbA1c is assayed using a central laboratory at screening V1 (Week -1), V3 (Day 180), and V4 (Day 360) (see [Section 1.2](#)).

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The visit schedule and procedures/assessments listed in the “Study Flow Chart” ([Section 1.2](#)) are not repeated in this section. The aim of this section is to provide details on how some of the procedures/assessments have to be performed.

This is an outpatient study and consists of a minimum of a screening visit followed by 3 on-site visits and without routinely scheduled other visits or phone-call visits. In this “real world trial” additional, optional on site visits and phone call visits for “standard of care” should be scheduled whenever considered necessary by the investigator and consistent with usual practice and local standards of care. These additional “standard of care visits” are for the routine care of the patient and are not part of the trial visit schedule. Some of these visits may be to monitor and support the progress of insulin titration according to Investigator discretion or may be related to other aspects of diabetes management or general medical care.

Retesting of HbA1c in central laboratory is allowed where the HbA1c measured in Central Laboratory is unexpectedly lower than 8% and not consistent with local laboratory done prior to screening.

If the patient has HbA1c outside of inclusion range, they may be rescreened if the HbA1c is greater than 11% since they would be expected to improve under their physicians care. HbA1c rescreening is not allowed where there is the potential for patients to allow their control to deteriorate.

Patients may be screen failed if they miss the window for randomization and can then be rescreened.

Patients to be rescreened are reviewed by Sponsor and approved on a case by case basis.

All on-site visits should take place in the morning. The patient needs to be in fasting conditions at on site visit, V1, screening visit, (Week-1) and also for V3 (Day 180, baseline), and V4 (Day 360), or at early discontinuation from IMP. Patient is required to come to the visit after a fasting period of at least 8 hours: during this time, only water or tea without sugar or sweetener and without milk is allowed. No coffee, no other beverages are allowed.

Visit window: from the screening visit, (V1, Week -1), V2 (Day 1) until the primary efficacy endpoint visit (Day 180), visits should occur within ± 30 days. End of treatment (Day 360) may occur within ± 30 days. If one visit date is changed, the next visit should occur according to the original schedule.

Patients in the US do not need to bring their used or unused pens to visits other than EOT visit as a log of insulin pens will not be used to assess compliance. Patients in Canada need to bring their used and unused pens to the site when IMP will be dispensed by the site and to the EOT visit.

For a complete list of procedures scheduled for each study visit please refer to the Study flowchart ([Section 1.2](#)). The aim of the sections of the “Visit Schedule” as well as “Assessment Methods” in ([Section 9](#), [Section 10.1](#)) is to detail procedures to be performed.

Patients who stop treatment early should be seen as soon as possible for an early end of treatment visit when 180 day assessment is completed and an EOT page in the CRF.

All data in the trial visits are reviewed by the clinician at the site who is qualified in the management of type 2 diabetes and initiation of insulin treatment.

10.1.1 Screening Period

The duration of the screening period is up to 1 week from Visit 1 (Week –1) to V2 (Week 0) such that patients must be randomized within 1 week of screening.

Patients will be screened at Visit 1 after signature of the informed consent form. All laboratory tests measured at central laboratory needed for checking the exclusion criteria of the patients will be performed at V1. Patients who meet the inclusion criteria and who have no exclusion criteria as noted in, [Section 7.1](#), will be randomized at V2 (Day 1).

The IVRS/IWRS will be contacted at V1 for notification of screening and for patient number allocation.

10.1.1.1 On-site Visit 1 (Week -1) Screening visit

The following procedures/assessments will be performed at the visit 1 (Week-1):

- Obtaining the informed consent:
 - The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration. Written information will be provided to the patient. Written informed consent must be signed by the patient and investigator prior to any investigations.
- IVRS/IWRS notified (allocation of patient number, registration of screening, collection of demographic information).
 - The patient number is composed of a 9-digit number containing the 3-digit country code, the 3-digit center code and the 3-digit patient chronological number (which is 001 for the first patient screened in a center, 002 for the second patient screened in the same center etc).
- Assessment of inclusion/exclusion criteria.
- Demographics (age, gender, and ethnic origin).
- Patient’s medical (including detailed cardiovascular) and surgical history.
- History of type 2 diabetes treatment including documentation of insulin treatment regimen, and microvascular complications (eye, kidney) and their treatments.

- Concomitant medication history.
- Prior medication history, particularly as it relates to diabetes medications.
- Physical examination including vital signs (SBP and DBP including in sitting position, heart rate).
- Body height and weight.
- Laboratory testing by central laboratory:
 - HbA1c and FPG,
 - Serum pregnancy test in women of child bearing potential,
 - Safety laboratory; serum creatinine and LFT (please refer to [Section 9.2.3.6](#)).
- Instruction on recording information related to hypoglycemia in e-diary or on paper back up form, instruction on recording routine SMPG recommended by site either in e-diary or a paper diary per usual site practice, and AE reporting, (report any events that may occur after signing informed consent).
- DTSQs ([Appendix D](#)), Hypoglycemia Patient Questionnaire ([Appendix H](#)), and PAM ([Appendix F](#)) are administered at the screening visit completed and collected at the site.

10.1.1.2 Baseline Visit 2 (Week 0, Day1) +/-7 days

Patients meeting all inclusion criteria and with no exclusion criteria at the end of the screening period (based on data collected at the screening visit V1 (Week -1) are eligible to be randomized and can participate in the study.

For the complete list of procedures scheduled for this visit, please refer to the study flowchart [Section 1.2](#)) and for detailed description of assessments.

At this visit, the patient does not need to be fasting.

During the visit;

- Concomitant medications are reviewed.
- Patient diaries, both paper and electronic, are reviewed for hypoglycemia and AE/SAE by the Investigator or Sub-Investigator who are qualified and familiar with the study and then entered into the e-CRF.
- Dispensation of Bluetooth enabled glucometer, e-diary, training materials and supplies
- Training is provided for use of glucometer and e-diary. IVRS is called to randomize the patient.
- Diet and lifestyle counseling is provided according to the routine custom of the practice.
- DTSQs and the Hypoglycemia patient questionnaire will be completed
- In the US, patients will be provided with a prescription for Toujeo or the control insulin and a “smart card” for obtaining the insulin at a commercial pharmacy.

- Training is provided by the site investigator or site staff regarding insulin pen use.
- A patient card, including emergency contact details and treatment arm will be provided to every patient who participates in the study.
- Patient will be invited to be enrolled into the Toujeo PSP for those patients randomized to Toujeo. Patients may also choose to participate in other PSP available to them. Data on enrollment in a PSP will be collected at this visit.
- Patients are provided glycemic targets and guidance on dose adjustment at the discretion of the Investigator and consistent with local practice guidelines and recorded in the clinical source documents. This information is not recorded in the e-CRF.
- IVRS/IWRS notified
- At Canadian sites, process of dispensing insulin is discussed and first insulin may be provided by site.

10.1.1.3 Visit 3 (Day 180) +/- 30 days

- Vital signs (SBP and DBP, heart rate) and weight.
- Physical examination.
- Laboratory testing done by central laboratory:
 - HbA1c and FPG.
- Concomitant medications are reviewed.
- Patient diaries, both paper and electronic, are reviewed for hypoglycemia and AE/SAE by the Investigator or Sub Investigator who are qualified and familiar with the study and then entered into the e-CRF.
- Insulin dose the day of the visit is recorded in the source and e-CRF.
- DTSQ_s, Hypoglycemia Patient Questionnaire, Patient and Provider Global Effectiveness Scales ([Appendix C](#)) are completed.
- Health Care Utilization Forms are completed
- Urine pregnancy test at site in WOCBP.
- IVRS/IWRS notified

10.1.1.4 Visit 4 (Day 360) +/- 30 days

- Vital signs (SBP and DBP, heart rate) and weight.
- Physical examination.
- Laboratory testing done by central laboratory:
 - HbA1c and FPG.
- Concomitant medications are reviewed.

- Patient diaries, both paper and electronic, are reviewed for hypoglycemia and AE/SAE by the Investigator or Sub Investigator who are qualified and familiar with the study and then entered into the e-CRF.
- Insulin dose the day of the visit is recorded in the source and e-CRF.
- DTSQ_s, DTSQ_c Hypoglycemia Patient Questionnaire, Patient and Provider Global Effectiveness Scales are completed.
- Health Care Utilization Forms are completed
- Urine pregnancy test at site in WOCBP.
- IVRS/IWRS notified

10.1.1.5 *Unscheduled phone visits*

Under certain circumstances, sites will be requested to contact patient to obtain additional safety information which may not have been collected due to the infrequent schedule of trial visits

- To review hypoglycemic events to obtain clinical information necessary for ADA classification
- To review severe or serious hypoglycemic events
- To collect missing information regarding SAE

10.1.1.6 *Glucose review at Day 45 and Day 90*

Sites are encouraged to review hypoglycemic events in the web based portal (Trial Manager) at approximately Day 45 and Day 90.

10.1.1.7 *“Standard of Care” visits*

- Laboratory testing done at discretion of investigator by local labs, and are not recorded in CRF
- Patient diaries, both paper and electronic (Trial Manager), are reviewed for hypoglycemia and AE/SAE by the Investigator or Sub Investigator who are qualified and familiar with the study and then entered into the e-CRF.

During these routine, “standard of care” visits” the physician records the reason for the visit and any trial actions taken in the medical record. Visit are not recorded in IVRS; visit is entered as an office visit in e-CRF form for capturing utilization data and any hypoglycemia and AE/SAE noted at the time of these visits are entered into the dedicated e-CRF pages for these events. No additional clinical information is entered into the data base and these visits are not considered part of the trial visit schedule. Visits should be documented as per usual for the practice site in their clinical record. The reason for the visit may be recorded as an AE if appropriate.

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in patient's file

Evaluations recorded in the e-CRF must be supported by appropriately signed source documentation related but not limited to the following:

- Agreement and signature of informed consent form with the study identification and any privacy forms.
- Study identification (name).
- Patient number, confirmation of randomization.
- Medical, surgical, diabetes history, including information on:
 - Demography, inclusion and exclusion criteria,
 - Comorbidities,
 - Calculation of HEDIS assignment worksheet, if available,
 - Last participation in a clinical trial,
 - Contraception method for WOCP,
 - Previous and concomitant medication.
- Dates and times of visits and assessments including examination results.
- Vital signs, height, body weight, laboratory reports.
- Adverse events and follow-up:
 - In case of SAE, the site should file in the source documents at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature study discontinuation (if any) and reason.
- Office notes related to the ongoing routine clinical care of this patient to include:
 - Nursing and other clinical staff notes,
 - Dietician's and diabetes educators notes,
 - Physician's notes.

10.2.1.1 Source data verification requirements for screen failures

For screen failure patients, the following source data must be verified: patient's identification details, the informed consent signed by the patient, the study identification (name), dates of study visits and the main reasons for screen failure. In addition, target HbA1c assigned is also recorded.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. Any IMP discontinuation should be fully documented in the e-CRF.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

It is in the interest of the patient to monitor plasma glucose during the temporary discontinuation period, therefore SMPG or other regular determination of plasma glucose is to be performed and documented.

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages when considered as confirmed.

Temporary treatment discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the patient. Use of a different insulin during the time of temporary treatment discontinuation is recorded (such as during a hospitalization) with the name and doses recorded in the CRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time. This is done consistent standards for withdrawing a drug and according to the experience of the investigator.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to determine the reasons for treatment discontinuation and this should be documented in the e-CRF.

The following reasons lead to permanent discontinuation:

- At the patient's own request.
- If, in the investigator's opinion, continuation with the administration of the study treatment would be detrimental to the patient's well-being.
- Inter-current condition that requires permanent discontinuation of the study treatment (eg, laboratory abnormalities according to the decision tree in [Appendix B](#) as long as the abnormality persists and if the casual relationship of the concerned event and the IMP is possible according to the Investigator's best medical judgment).
- Pregnancy.
- Specific request of the sponsor.

Any abnormal laboratory value or ECG will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

For patients who prematurely discontinue the IMP, the end-of-treatment visit assessments for Day 360 will be done ([Section 10.3.2](#)) as soon as possible after stopping the IMP. However, the patients will be informed that they should continue to report hypoglycemia events in their e-Diary, and come back to the Day 180 visit for HbA1c assessment and hypoglycemia review with investigator and encouraged to continue to Day 360, end of the extension period).

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, to a minimum of Day 180 or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. If possible, the patients are assessed using the procedure normally planned for the end-of-study visit.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient to determine his/her health status according to local standards of care. Patients may continue to have their care provided by the site physician without participating in the trial.

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

The treatment period is over when the last dose of IMP is received. An EOT visit is completed including recording reason for EOT. Patients are not allowed to “switch” to insulin in the other treatment arm and insulin will not be reimbursed by Sponsor after EOT. Patients are encouraged to continue in trial off treatment and in this case the insulin is recorded on the Conmed CRF page.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
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.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm,
 - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
 - Convulsions (silures, epilepsy, epileptic fit, absence, etc),
 - Development of drug dependence or drug abuse,
 - ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN,
 - Suicide attempt or any event suggestive of suicidality,

- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
- Bullous cutaneous eruptions,
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies),
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

The AESI for this study:

- Increase in alanine transaminase (ALT) (see the "Increase in ALT" flow diagram in [Appendix B](#) of the protocol) which would only be identified by local laboratory as there is no lab testing by Central Laboratory during the trial
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP.
 - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see [Section 10.4.1.2](#)).
 - In the event of pregnancy in a female participant, IMP should be discontinued,
 - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP:
 - A symptomatic overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient and resulting in clinical symptoms and/or signs and considered a "significant overdose" by the Investigator. It will be recorded in the e-CRF as an AESI with immediate notification "Symptomatic OVERDOSE (accidental or intentional)" in all cases and will be qualified as an SAE only if it fulfills the SAE criteria.

Asymptomatic overdose (accidental or intentional) with the IMP/NIMP is defined as any “significant” overdose, without clinical symptoms and/or signs, either suspected by the investigator or spontaneously notified by the patient. It will be recorded as an AE “Asymptomatic OVERDOSE (accidental or intentional)”. The event must be clinically relevant and be more of an event than just using a titration dose increase compared to what had been previously prescribed. Asymptomatic overdose does not require immediate notification.

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

There are no waivers from expedited reporting of serious health events to health authorities in this trial.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.
- AEs may also be identified by pharmacists, and providers other than the provider primarily responsible for the diabetes management such as specialists, nurse educators. It is the responsibility of the patient to keep a record of their AEs and the site investigator will enter these AEs from these multiple providers.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s). For events reported through the PSP vendor, global safety officer (GSO) is responsible for identifying potential SAE that are not included in the data base and whether the SAE was caused by the IMP.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. When treatment is prematurely discontinued, the patient’s observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
 - Symptomatic and/or
 - Requiring either corrective treatment or consultation, and/or
 - Leading to IMP discontinuation or modification of dosing, and/or
 - Fulfilling a seriousness criterion, and/or
 - Defined as an AESI.

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in [Section 10.4.4](#), even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

Instructions for AE reporting are summarized in [Table 1](#).

10.4.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Appendix B](#).

The following laboratory abnormalities are not routinely monitored. When abnormal labs are identified by local laboratory during the reporting of an AE, they are monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia,
- Thrombocytopenia,
- Increase in ALT,
- Acute renal insufficiency,
- Suspicion of rhabdomyolysis.

Table 1 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)				No
		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No
		ALT \geq 3 ULN (if baseline ALT<ULN) and ALT \geq 2 x baseline (if baseline ALT \geq ULN)	Yes	Yes	Yes

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.
- There are no specified AESIs.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected [please refer to the package].

Any other AE not listed as an expected event in the Package Insert or in this protocol will be considered unexpected.

As this is an open label study, no un-blinding of SUSARs is necessary.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

Sponsor will review potential SAEs identified through the COACH Patient Support Program.

Review of claims data for SAE is not planned for the study as it will be included as a separate analysis; as the analysis will be done after the 12 month whole treatment period and will be contained in a report separate from the main study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypoglycemia

Severe symptomatic hypoglycemia

Severe symptomatic hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others.

Note that “requires assistance” means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a “requires assistance” incident.

Severe symptomatic hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria. All events of seizure, unconsciousness or coma must be reported as SAEs.

Documented symptomatic hypoglycemia

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L). In addition, hypoglycemia episodes with a plasma glucose of < 54 mg/dL (3.0 mmol/L) will be analyzed.

Clinical symptoms that are considered to result from a hypoglycemic episode are, eg, increased sweating, nervousness, asthenia, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, and coma.

Probable symptomatic hypoglycemia

Probable symptomatic hypoglycemia is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L); symptoms treated with oral carbohydrate without a test of plasma glucose.

Patients will be instructed to measure finger stick plasma glucose levels prior to the administration of carbohydrates whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose rescue prior to confirmation, and then a glucose measurement should be performed as soon as safe, with appropriate diary documentation. Details on hypoglycemia episodes will be captured in the patient e-diaries and then available in the vendor web based portal. Patients will contact the sites as soon as possible following severe events to review the details and decide on any necessary measures to be taken.

Symptomatic hypoglycemia episodes will be documented on the Low Blood Glucose Event (LBGE) page in the clinical data base. Symptomatic hypoglycemia events fulfilling the criteria of a SAE will also be documented on AE and SAE forms form in the e-CRF.

For discussion of endpoints related to hypoglycemia, see [Section 9.2.3.1](#)

10.6.2 Local safety

In case the investigator or the patient recognizes any sign related to local safety at the injection site this should be recorded on the standard AE page in the e-CRF.

In case a patient experiences an allergic reaction or an allergic-like reaction this has to be reported as an adverse event and recorded in the e-CRF on the standard AE form.

Sometimes transient injection site reactions, irritant in nature may occur requiring no intervention and are of dubious significance. These reactions would not be considered to be allergic reactions. A Product Technical Complaint should be completed if a problem with the device is noted.

10.6.3 Follow-up of laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities are provided in [Appendix B](#). This is applicable to abnormal laboratories at screening done in Central Laboratory or local laboratories obtained related to a reported AE.

10.6.4 SMPG

Routine SMPG is done by the patient according to guidelines set by the investigator to support titration. No specific safety instructions are provided and SMPG is monitored by the site and not recorded in the clinical data base.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size (1662 patients per treatment group) calculations take into account one Interim Analysis performed after 1800 randomized patients having completed their 6 months visit. They are based on superiority testing of the primary efficacy variable of the proportion of patients reaching individualized HbA1c target at Month 6 without a documented symptomatic (BG \leq 70 mg/dl) or severe hypoglycemic event at any time of day from baseline to Month 6, with the following assumptions:

- Individualized HbA1c target attainment per HEDIS criteria of $<8\%$ if older or presence of medical comorbidities, or otherwise $<7\%$,
- An absolute difference of 5.5% in favor of Toujeo in patients assigned a target HbA1c $< 7\%$, assuming a 30.1% rate in the Toujeo arm, based on data from the EDITION 3 study,
- An absolute difference of 5.4% in favor of Toujeo in patients assigned a target HbA1c $< 8\%$, assuming a 55.8% rate in the Toujeo arm, based on data from the EDITION 3 study,
- An absolute overall (weighted average) difference of 5.5% in favor of Toujeo for all patients combined, assuming that 70% of the study patients would have a target HbA1c $< 7\%$, and 30% would have a target HbA1c $< 8\%$, based on data from a commercially available database,
- A maximum overall response rate of 33% in the comparator basal insulins arm,
- A 2-sided chi-squared test at the 5% significance level, with 90% power,
- All patients will be eligible for the primary endpoint analysis.

As a logistic model will be used for the primary analysis, it is anticipated that the power will be higher due to reduced estimate variability compared with the chi-square test. Calculations were made using nQuery Advisor 6.01.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

All randomized patients will be included in the Intent-to-Treat Population.

Patients will not be randomized more than once.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent-to-treat population

- ITT population: all randomized population analyzed according to the treatment group allocated by randomization.

11.3.2 Safety population

- As treated: defined as all randomized patients who actually received at least 1 dose or part of a dose of IMP, analyzed according to the treatment actually received. In addition:
 - Nonrandomized but treated patients will not be part of the safety population. This is a post marketing real world trial with commercially available insulin so that nonrandomized but treated patients are not considered part of the trial and safety data is neither collected nor presented.
 - Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

The duration of exposure during the study will be the total number of days of administration of IMP, accounting for temporary drug discontinuation.

The duration of exposure to the open-label IMP during the study is defined as:

$$(\text{Date of the last IMP administration} - \text{date of the first IMP administration}) + 1.$$

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

A superiority test will be performed at interim analysis (2-sided, $\alpha=0.010$) and at final 6-month analysis (2-sided, $\alpha=0.046$) to compare the proportion of patients reaching individualized HbA1c target at 6 months without documented symptomatic ($BG \leq 70$ mg/dl) or severe hypoglycemia between treatment groups using a logistic model with log link, adjusting for HbA1c target and other stratification factors used at randomization: SU use ever (y/n), GLP-1 RA

use ever (y/n), and baseline HbA1c (as continuous). In a sensitivity analysis a multivariate analysis will be performed, adding the following baseline characteristics such as BMI, Patient Activation Measure (PAM) as an assessment of patient engagement, duration of diabetes and age.

Patients with missing HbA1c data at 6 months will be regarded as not having reached HbA1c target.

In order to examine the consistency of this analysis, the individual components of HbA1c target attainment and absence of any documented symptomatic ($BG \leq 70$ mg/dl) or severe hypoglycemia will also be evaluated. Each individual component will be compared between treatment groups using logistic regression, adjusting for randomization strata and other baseline characteristics as clinically appropriate.

Further, a predictive subgroup identification method will be employed to identify subgroups of potential responders.

Analyses of secondary efficacy endpoints ([Section 9.2.1](#)).

Persistence:

- Treatment persistence will be determined based on vendor database that would be responsible for managing and administration of the study drugs (Toujeo, Lantus, Levemir) from the vendor database administering the study drugs, information on prescription fill date, quantity dispensed, days of supply, number of units dispensed, prescription refill dates will be obtained in estimation of treatment persistence and discontinuation.
- In addition, for US patients, a medication possession ratio will be assessed for patients based on number of days that patients had possession of study drug based on prescription date and days of supply. A MPR of 80% would be indicative of patients being persistent on study medication. Those not persistent will be considered discontinued on their study medication.
- Treatment persistence will be summarized descriptively (N, Mean, SD, Median, Min, and Max).

Efficacy Endpoints:

The change in HbA1c from baseline to 6 months will be analyzed using a mixed-effect model with repeated measures (MMRM) approach under the missing at random framework, using an adequate contrast at Month 6. The model will include fixed categorical effects of treatment arm, visit, treatment-by-visit interaction, HbA1c target and other randomization strata; SU use ever (y/n), GLP-1 RA use ever (y/n), and baseline A1c (as continuous), as well as baseline HbA1c-by-visit interaction.

The change in fasting plasma glucose and bodyweight from baseline to 6 and 12 months will be analyzed in a similar fashion to the change in HbA1c.

The proportion of patients with individualized HbA1c target attainment without hypoglycemia will be analyzed as described for the primary endpoint.

11.4.3 Analyses of safety data

The summary of safety and tolerance results will be presented by treatment group ([Section 9.2.3](#)).

All safety analyses will be performed on the Safety population using the following common rules:

- The baseline value is defined as the last available value prior to the first injection of IMP,
- There are no pre-defined Potentially Clinically Significant Abnormality (PCSA) values for this study,
- There are no safety endpoints which are adjudicated.

The baseline values for all safety analyses are defined as the last available value prior to the first dose of randomized treatment. There are no quantitative safety parameters based on central laboratory measurements. The last on-treatment value is defined as the value collected at the same day/time of the last dose of randomized product. If this value is missing, this on-treatment value is the closest one prior to the last dose intake. Given the short half-life for duration of action of insulin, the TEAE reporting period is one day after last administration of IMP.

The analysis of the safety variables is essentially descriptive and no systematic testing is planned. Relative risk for the Toujeo arm of the study versus the comparator basal insulins group, and their 95% CI may be provided, if relevant.

Hypoglycemia

The incidence of hypoglycemia will be analyzed using logistic regression, adjusting for randomization strata and other baseline characteristics as clinically appropriate and if the model permits. The rate per patient-year of hypoglycemic events will be analyzed using an over-dispersed Poisson regression model, adjusting for randomization strata and other baseline characteristics as clinically appropriate and if the model permits.

11.4.4 Analyses of Patient Reported Outcomes

Self-reported patient satisfaction and hypoglycemia: Satisfaction scores at 6 and 12 months will be compared between treatment groups using a MMRM approach as described for the continuous efficacy variables. To adjust for the baseline differences between treatment groups, logistic regression will be conducted, adjusting for randomization strata of HbA1c target, SU use ever (y/n), GLP-1 RA use ever (y/n) and baseline A1c (as continuous).

Global Effectiveness Scale (GES): At each study endpoint, the proportion of patients and providers who reported “Excellent” or “Good” at 6 and 12 months will be analyzed using CMH tests adjusting for randomization strata.

11.4.5 Health-related Quality of Life/health economics variables

Health resource utilization for each treatment group will be analyzed by descriptive analysis. Multivariate analysis will be used to evaluate the difference in health resource utilization and cost between treatment groups with t adjustments for patient level data from CRF to include baseline characteristics and comorbidities as covariates.

11.5 INTERIM ANALYSIS

One interim analysis is planned for the purpose of efficacy to provide an early evaluation of Toujeo effectiveness, when approximately 1800 patients (54.2% information fraction of targeted sample size) have completed their 6-month (Day 180) visit.

Using a group sequential approach with a Gamma(-3) alpha-spending function and an overall two-sided alpha-level of 0.05, the two-sided nominal significance level is 0.010 at interim analysis, and 0.046 at final analysis.

If the targeted sample size (1800) cannot be reached, it could be considered to include a lower number of patients, however not below 1700. In this case, the nominal significance level to be spent at interim and at final 6-month analyses would be recalculated accordingly before the database lock for IA.

Overwhelming efficacy will be shown at interim analysis if the efficacy boundary is met, ie, if the two-sided p-value for comparison of primary composite endpoint incidence is below 0.010, with a difference in favor of Toujeo between percentages of patients reaching the primary composite endpoint. The corresponding power to show overwhelming efficacy at interim analysis under the alternative hypothesis is of 45%.

Scenario 1: If overwhelming efficacy is shown:

- The recruitment would be stopped (total sample size at that time estimated to be between 2600-3000 patients,
- The patients already enrolled would continue the study as planned,
- The results will be disclosed to the Sponsor and a communication plan to protect clinical data integrity is detailed in the DMC charter.

Scenario 2: If overwhelming efficacy is not shown:

- The study would continue as planned
- The Sponsor would not have access to any unblinded data,
- No results would be communicated.

For the interim analysis, analyses will be performed by an independent statistician external to the Sponsor. Results will be delivered directly to the independent Data Monitoring Committee for review.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Sub investigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form and/or privacy form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

This informed consent contains a section allowing for release of claims data from the payer to the sponsor that may be signed anytime up until end of trial visit. The informed consent describes the use of this information in the study analysis and that the claims data is linked to the clinical data base for purpose of analysis.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

A separate privacy form request may be necessary and if required by local law, the form will be completed and signed by the patient.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be prescribed at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC and privacy board at least annually and a summary of the clinical trial's outcome will be sent at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, concomitant therapy use and quality of data. In addition, the monitoring team may as a safety and a compliance issue, review the hypoglycemia data obtained by the patient with the sponsor provided glucometer and with results stored in a web based portal as an electronic source document.

In Canada, monitoring will also include patient compliance with the IMP regimen and IMP accountability.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, and documents provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Sub-investigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub-investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio
- Patient enrollment is unsatisfactory
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
- Non-compliance of the Investigator or Sub-investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP
- The total number of patients are included earlier than expected

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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