AMENDED CLINICAL TRIAL PROTOCOL NO. 01

COMPOUND: Toujeo / insulin glargine / HOE901-U300

A Randomized, Active-Controlled, Parallel Group, 16-Week Open Label Study Comparing the Efficacy and Safety of the Morning Injection of Toujeo (Insulin Glargine-U300) Versus Lantus in Patients with Type 1 Diabetes Mellitus

STUDY NUMBER: LPS14587

VERSION DATE / STATUS: 02 August 2016 / Approved

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	Sanofi US Services Inc 55 Corporate Drive Bridgewater, NJ 08807 USA
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: HOE901-U300 (Toujeo insulin glargine)	**STUDY No: LPS14587**
TITLE	A randomized, active-controlled, parallel group, 16-week open label study comparing the efficacy and safety of the morning injection of Toujeo (insulin glargine U300) versus Lantus in patients with type 1 diabetes mellitus.
INVESTIGATOR/TRIAL LOCATION	United States: Multicenter
PHASE OF DEVELOPMENT	4
STUDY OBJECTIVE(S)	**Primary objective:** To demonstrate that morning injection of Toujeo compared to Lantus will provide better glycemic control evaluated by Continuous Glucose Monitoring (CGM) in adult patients with type 1 diabetes mellitus. **Secondary objective(s):** To demonstrate that treatment with Toujeo compared to Lantus will provide • lower incidence rate of nocturnal symptomatic hypoglycemia, • better glucose control coverage during the last hours of CGM before next basal-insulin dosing; • less variability in CGM profile.
STUDY DESIGN	A multicenter, randomized, active-controlled, parallel group, 16-week open-label study. The study consists of an up to 4-week screening and CGM training period and a 16-week treatment period. Blinded CGM data (blinded to both patients and investigators) will be collected at the end of screening (Week -2 to 0) and the end of treatment (Week 15-16) for endpoint analyses. During the baseline training period, patients will wear a blinded CGM device for 7 consecutive days to generate a minimum 4 days of usable CGM data to be eligible for randomization. If a patient fails the first attempt for any reason, he/she will be retrained for CGM conduct and complete another course of blinded CGM. Patients satisfying the inclusion/exclusion criteria and CGM requirements will be randomized 1: 1 to morning injection of either Toujeo or Lantus. Given the potential impact of certain variables on the primary endpoint, randomization will be stratified by baseline HbA1c (<8, ≥8), frequency of the basal insulin injections at screening BID vs QD, current CGM use (yes/no) and mealtime insulin titration algorithm followed. Dosing will be once daily in the morning, defined as the time period between waking up and breakfast. The injection time will be discussed between the investigators and patients at randomization and should be kept consistent at the same time each day. The patients will also be asked to maintain a log of the time of injection. During the entire study starting after screening, patients will perform Self-Monitoring of Plasma Glucose (SMPG) as specified in the study flow-chart and the protocol. SMPG readings will be used to guide insulin dose- titration for optimal glycemic control and the SMPG profiles will be collected for efficacy analyses. Appropriate dose titration of basal and mealtime insulin will be implemented

	as outlined in the dose regimen section. Titration of basal insulin will be allowed until Week14 of the study after which, the Toujeo/Lantus dose should remain unchanged during the period of the CGM collection (Week 15 or 16), while meal-time insulin dose can still be adjusted as appropriate. During Week15, patients will wear a blinded CGM device for 7 consecutive days to generate a minimum of 4 days of useable CGM data. If a patient fails the first attempt for any reason, he/she will be retrained for CGM conduct and complete another week of blinded CGM data collection during Week 16. At the end of the study, the patients will be followed-up within 2 (+2) days to collect post treatment safety information.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Adult patients (male and female) with type 1 diabetes mellitus • Signed written informed consent **Exclusion criteria:** • Age <18 years or >70 years; • Fasting c-peptide ≥0.3nmol/l as per source document or central lab test at Visit 1, • HbA1c ≤6.5% or ≥10.0% via central lab test at Visit 1, • Patients who experienced none episode of documented symptomatic and/or severe hypoglycemia (as per the ADA classification) during the past month prior to screening, • Patients who experienced >1 episode of severe hypoglycemia resulting in coma/seizures during the last 12 months before screening, • Patients receiving less than 1 year treatment with basal plus mealtime insulin, • Using any basal insulins other than long acting-insulin analogs (i.e. Lantus, Toujeo, Levemir or Tresiba) in the past 3 months before screening, • Requiring >80 U/day basal insulin analogs and/or not on stable dose (± 20% total dose) within 30 days prior to screening, • Using fewer than 2 injections of rapid-acting insulin analog per day within 30 days prior to screening, • Using human regular insulin as mealtime insulin within 30 days prior to screening • Using an insulin pump during the last 6 months before screening, • History of unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema likely to require treatment (eg, laser, surgical treatment or injectable drugs) during the study period, • Pregnant or breast-feeding women or planning pregnancy during the duration of the study, • Use of any other investigational drug(s) within 1 month or 5 half-lives, whichever is longer prior to screening, • Inappropriate CGM use during screening period evidenced by failure to obtain a minimum of 4 days of usable records by the end of screening, • Non-compliance with SMPG performance evidenced by failure to demonstrate at least 5 days of 5-point SMPG records by the end of screening.

Total expected number of patients	Approximately 616 patients randomized, aiming for approximately 524 patients with evaluable data. Approximately 100 study sites.
STUDY TREATMENT(s)	Tested drug: Toujeo (HOE901-U300) Control drug: Lantus (HOE901-U100)
Investigational medicinal product(s) **Formulation:**	**Testing drug: Toujeo (Insulin glargine -U300)** Toujeo will be supplied for subcutaneous (SC) injection as a sterile, non-pyrogenic, clear, colorless solution in a 1.5 mL Toujeo SoloStar disposable prefilled pen (450 Units/1.5 mL). Application of the drug is done using an injection pen device allowing dose setting in the range of 1-80 U with 1 U increment. Mixing of Toujeo with other insulins is not allowed nor dilution. **Control drug**: **Lantus (Insulin glargine-U100)** Lantus will be supplied for SC injection 100 U/mL in 3 mL cartridges assembled in a pen-injector. Lantus SoloStar prefilled (disposable) pen will be used for this study. The disposable SoloStar pen-injector allows for a dose setting in the range of 1-80 U with minimum dose increment of 1 U. Mixing of Lantus with other insulins is not allowed nor dilution.
Route(s) of administration:	Subcutaneous injection.
Dose regimen:	Toujeo and Lantus will be self-administered by SC injection once daily in the morning, which is defined as the time period between waking up and pre-breakfast. The clock time for the morning injection (hh:mm) will be established at the discretion of the patient/investigator at the time of randomization and will be maintained for the duration of the study. • On the randomization day (Day 1), the initiation dose of glargine (Toujeo and Lantus) is the patient's current dose of their basal-insulin analogs. For patients taking the basal insulin in any time other than morning injection previously, they should switch the dosing time to morning injection during screening period. • During the treatment period, dose of Toujeo and Lantus) will be titrated in dose steps outlined in the table below to achieve glycemic target and minimize the potential risk of hypoglycemia. • The target range for fasting SMPG is 80–100 mg/dL (4.4-5.6 mmol/L). • Dose adjustment for insulin glargine is based on the mean fasting (pre-breakfast/pre-injection) SMPG values of the last 3 days without related hypoglycemia. • For each titration step, the insulin dose increment should not exceed 10% of the existing glargine daily dose, irrespective of the mean fasting SMPG values, eg, for a daily dose of 30 U, the increment should be 3 U if the mean fasting SMPG is >120 mg/dl. • Titration of insulin glargine will be continued until the end of Week 14, after which patients will maintain a stable dose during the endpoint for blinded CGM collection (Weeks 15-16) except for dose reduction in the case of safety reasons (eg, basal insulin related severe hypoglycemia).

<table>
<tr><td></td><td>
<table>
<tr><th>Mean fasting SMPG values (last 3 days)</th><th>Insulin Glargine (U-100 or U-300) dose adjustments (U/day) [a]</th></tr>
<tr><td>≥120 (> 6.7 mmol/L)</td><td>+ 4 Units, or split to 2x2 U</td></tr>
<tr><td>≥100 and ≤120 mg/dL (>5.6 and ≤6.7 mmol/L)</td><td>+ 2 Units, or split to 2x1 U</td></tr>
<tr><td>Glycemic target: mean fasting SMPG between 80 – 100 mg/dL
80 and 100 mg/dL (4.4 and 5.6 mmol/L), inclusive</td><td>No change</td></tr>
<tr><td>≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)</td><td>-2 Units</td></tr>
<tr><td><60 mg/dL (3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode</td><td>-4 Units or at the discretion of the investigator or medically qualified designee</td></tr>
</table>
[a] Prior to additional basal insulin titration, mealtime insulin should be titrated to achieve a bedtime and pre-breakfast glucose delta <50 mg/dL.
</td></tr>
<tr><td>Noninvestigational medicinal product(s) (if applicable)</td><td>Patients in both treatment groups will continue with their current rapid-acting insulin analog (eg, insulin glulisine, insulin lispro or insulin aspart) during the study.</td></tr>
<tr><td>Formulation:</td><td>Solution for subcutaneous injection.</td></tr>
<tr><td>Route(s) of administration:</td><td>Subcutaneous injection.</td></tr>
<tr><td>Dose regimen:</td><td>

Patients will continue on their existing mealtime insulin (rapid-acting insulin analog) regimen at randomization.
The injection time and frequency of rapid-acting insulin will be at investigator’s discretion in accordance with the prescribing information.
During the treatment period, the doses of the mealtime insulin analog should be actively titrated to achieve and maintain the 2-hour postprandial SMPG in the range 130-180 mg/dL (7.2-10 mmol/L).
Dose adjustment of mealtime insulin will be allowed throughout the 16 weeks of treatment period, including the endpoint period for blinded CGM collection (Week 15-6) with the fixed doses of insulin glargine
Dose adjustment of mealtime insulin can be based on a pattern of post-meal SMPG data from the prior 3 days (simple titration) OR the carbohydrate content of the meal; both the recommended regimens are outlined below

</td></tr>
</table>

Simple titration: Titration of mealtime insulin based on a pattern of post-meal glucose median 130 </>180 mg/dl in the prior 3 days using the table below

Mealtime dose of Insulin	Pattern of Postprandial BG values <130 mg/dL[a]	Postprandial BG values >180 mg/dL[a]
≤10 Units	Decrease dose by 1 Unit	Increase dose by 1 Unit
≥11-19 Units	Decrease dose by 2 Units	Increase dose by 2 Units
≥20 Units	Decrease dose by 3 Units	Increase dose by 3 Units

[a] If more than one-half of the mealtime blood glucose (2-hours PPG) values for the week were above target.

OR

Carb counting: (insulin-to-carbohydrate ratio) group

Starting recommendation 1 unit to 15 grams carbs

Consider calculating insulin to carb (I:C) ratio = 500 / total daily dose (TDD) of insulin.

Mealtime dose of Insulin	Pattern of Postprandial BG values <130 mg/dL[a]	Pattern of Postprandial BG values >180 mg/dL[a]
1 unit/20 g	Decrease to 1 unit/25 g	Increase to 1 unit/15 g
1 unit/15 g	Decrease to 1 unit/20 g	Increase to 1 unit/10 g
1 unit/10 g	Decrease to 1 unit/15 g	Increase to 2 unit/15 g
2 unit/15 g	Decrease to 1 unit/10 g	Increase to 3 unit/15 g
3 unit/15 g	Decrease to 2 unit/15 g	Increase to 4 unit/15 g

[a] If more than one-half of the mealtime blood glucose values for the prior 3 days were above target.

Correction dose: Investigators will be provided an initial guideline of 1800/TDD as a correction factor, if applicable, in addition to investigator directed change in correction factor based on glucose patterns.

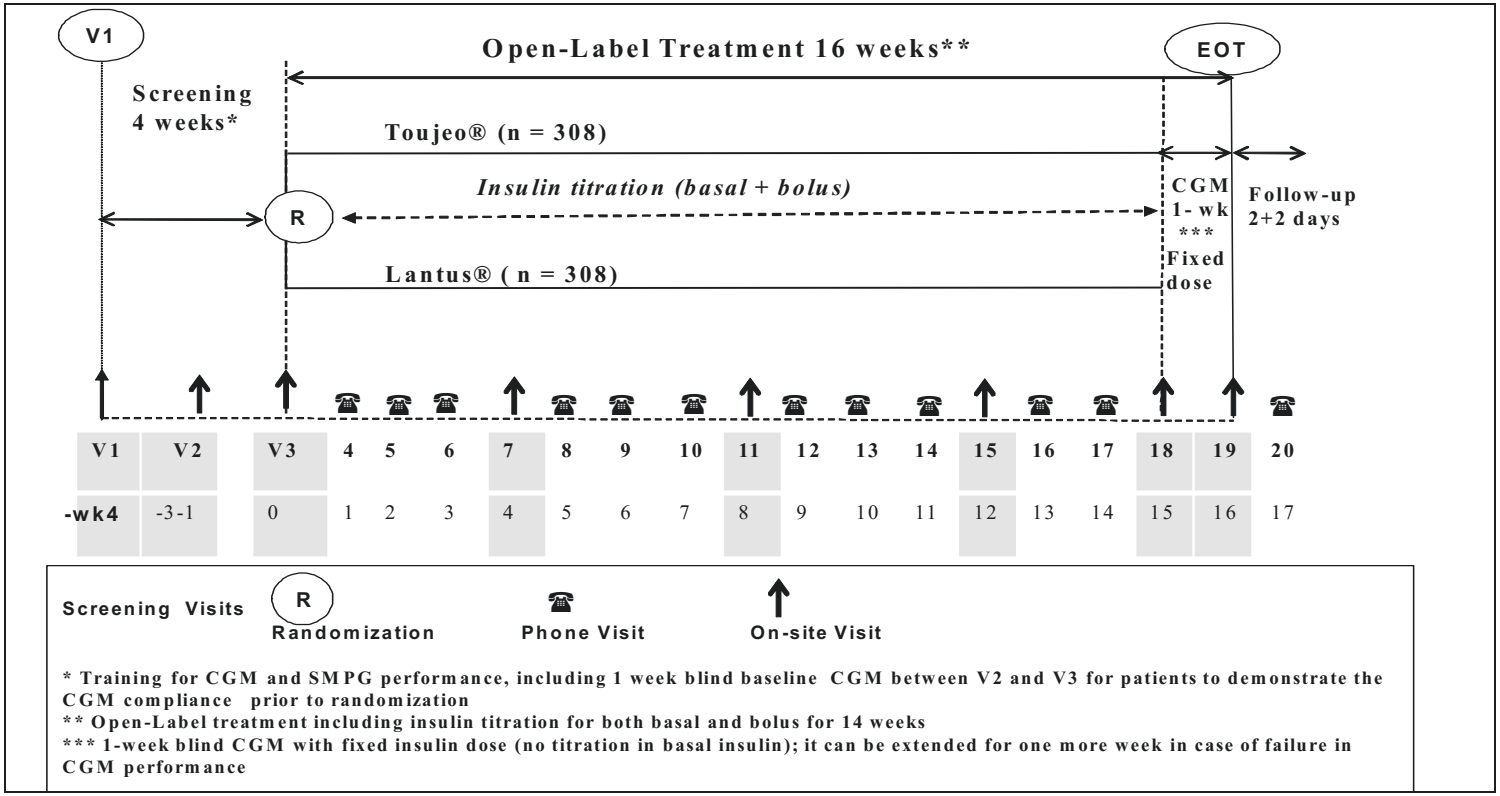
ENDPOINT(S)	**Primary endpoint:** • Percentage (%) of time plasma glucose in target range of 70-180 mg/dL (3.9-10 mmol/L) during Weeks 15-16, obtained from CGM. **Secondary endpoint(s):** • Incidence and rate of nocturnal symptomatic hypoglycemia, defined as an event with typical symptoms of hypoglycemia accompanied by SMPG ≤70 mg/dL (3.9 mmol/L) that occurs between 00:00 and 05.59 hours. • Percentage (%) of time glucose concentrations obtained by CGM within target range of 70-140 mg/dL (3.9-7.8 mmol/L) during the last 4 hours of CGM data collection prior to next day basal insulin injection. • Total, within day and between day coefficient of variation in glucose obtained from CGM. **Other endpoints:** • Frequency and distribution (nocturnal or 24 hours) of all hypoglycemia events analyzed by hypoglycemia categories (severe, documented symptomatic, asymptomatic, probable and relative) as defined in the publication ADA Workgroup on Hypoglycemia, 2015. • Additional CGM Endpoints (data obtained during Week 15-16) **:** - Percentage (%) of time glucose concentrations within the target range of 70-140 mg/dL (3.9-7.8 mmol/L) ☐ analyses on all- time (24 hours) CGM data, - Percentage (%) of time glucose concentrations ≤70 mg/dL (3.9 mmol/L) and <54 mg/dL (3 mmol/L) ☐ analyses on both all-time (24 hours) and nocturnal (00:00–05:59 hours) CGM data, - Percentage (%) of time glucose >140 mg/dL (7.8 mmol/L), >180 mg/dL(10 mmol/L) and > 250 mg/dL (13.9 mmol/l) ☐ analyses on both all-time (24h) and nocturnal (00:00–05:59 hours) CGM data, - Total, within day and between day coefficient of variation in glucose concentrations - Area under the glucose curve (AUC) of glucose concentration ≤70 mg/dL (3.9 mmol/L) - AUC of glucose concentration >180 mg/dL(10 mmol/L) • 7-point SMPG profiles (pre-prandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, and bedtime); • Change from baseline to study endpoint in HbA1c • Change from baseline to treatment endpoint in central lab FPG • Insulin dose (total, basal, mealtime/bolus, ratio of basal to bolus insulin dose) **Safety:** Evaluation of injection site reactions, hypersensitivity reactions, adverse events, serious adverse events (including hypoglycemic episodes associated with seizures, coma or unconsciousness etc) and vital signs.

ASSESSMENT SCHEDULE	The schedule of study-related procedures/assessments is detailed in the Study Flowchart. The study design and visit schedule is detailed in study flowchart Section 1.1.
STATISTICAL CONSIDERATIONS	**Sample size determination:** A sample size of 262 evaluable patients per treatment arm would provide at least 90% power to demonstrate superiority of Toujeo over Lantus in the percentage of time plasma glucose within the range of 70-180 mg/dL, using a 2-sided test with an α-level of 0.05.This is assuming an absolute difference of at least 4%, a standard deviation of 14%, and an expected value of 53% in the Lantus arm. This sample size would also provide at least 80% power to demonstrate a difference in the rate of documented symptomatic nocturnal hypoglycemia occurring at any point post randomization, assuming a rate ratio (Toujeo over Lantus) of at most 0.86 events per pt-year. **Analysis population:** Efficacy analyses will be performed on the modified Intent-to-Treat (mITT) population, which will comprise of all patients who are randomized and who have at least one post-baseline assessment for the endpoint of interest. Safety analyses will be performed on the safety population, which will comprise of all patients who receive at least one dose of study treatment. **Primary analysis:** The percentage of time glucose in target range 70-180mg/dL (3.9–10mmol/l) during weeks 15-16 (obtained from CGM) will be calculated based from the denominator of total time with valid data. The percentages will be summarized and analyzed for differences between treatment groups using a generalized linear model, adjusting for key baseline characteristics (duration of diabetes, BMI, age and baseline value) and randomization strata. **Analysis of secondary endpoints:** Continuous CGM endpoints will be analyzed using a generalized linear model as described for the primary endpoint. The change in HbA1c (and FPG) from baseline to endpoint will be analyzed using a mixed-effect model with repeated measures (MMRM) approach under the missing at random framework, using an adequate contrast at endpoint. The model will include fixed categorical effects of treatment arm, visit, treatment-by-visit interaction, randomization strata, and baseline HbA1c as covariate as well as baseline HbA1c-by-visit interaction. Other categorical CGM endpoints will be analyzed using the Chi-square or Cochran-Mantel-Haenszel test, including randomization strata. Fisher's Exact test will be employed if required. The incidence of hypoglycemia will be analyzed using logistic regression, adjusting for randomization strata and other baseline characteristics (duration of diabetes, BMI and age) 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 (duration of diabetes, BMI and age) as clinically appropriate and if the model permits.

DURATION OF STUDY PERIOD (per patient)	The study duration consists of: • Up to 4-week screening and training period including 1-2-week CGM performance (allow for re-training); • 14-week open-label, comparative treatment period allowing for dose titration in both basal and meal-time insulin; • 1-2 week blinded CGM collection with fixed dose of Toujeo or Lantus, • 2 days of post-treatment safety follow-up period after treatment completion or premature discontinuation of study treatment. The maximum study duration per patient will be around 20 weeks.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

	Screening and training			Treatment Period (15-16 weeks)																Follow up
Visit Windows: Visit 4 - 19: ± 3 days	1	2*	3	4[a] ☎	5[a] ☎	6[a] ☎	7	8[a] ☎	9[a] ☎	10[a] ☎	11	12[a] ☎	13[a] ☎	14[a] ☎	15	16[a] ☎	17[a] ☎	18[b]	19	20[a] ☎
Week	-4	-3 -1	(R)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	2+2 days
Informed consent	X																			
Inclusion/Exclusion criteria	X	X	X																	
Medical and surgical history; diabetes history	X																			
Physical examination, including neuropathy screening	X																			
Vital signs[c] and Body weight	X		X				X				X				X				X	
Height	X																			
Dispensation/collection of study diary	X	X	X				X				X				X			X	X	
Dispensation of study medication			X				X				X				X					
IMP compliance Check; collecting and counting used and unused pens							X				X				X			X	X	
IVRS call	X		X				X				X				X				X	
Randomization			X																	
Documentation and review of basal and bolus insulin dose	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Change from BID to QD basal insulin injection (if applicable)		X																		
CGM, SMPG:																				
Training and re-training: Glucometer, SMPG profiles, study diary	X	X	X				X				X				X			X		
Dispensation glucometer,	X																			
Dispensation CGM device; Blinded CGM[d]		X																X		
Upload CGM to PC			X																X	
Collect CGM device			X																X	
SMPG[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Upload SMPG to PC		X	X				X				X				X			X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Central Laboratory																				
HbA1c, Fasting plasma glucose (FPG)	X										X								X	

	Screening and training			Treatment Period (15-16 weeks)																Follow up
Visit Windows: Visit 4 - 19: ± 3 days	1	2*	3	4[a] ☎	5[a] ☎	6[a] ☎	7	8[a] ☎	9[a] ☎	10[a] ☎	11	12[a] ☎	13[a] ☎	14[a] ☎	15	16[a] ☎	17[a] ☎	18[b]	19	20[a] ☎
Week	-4	-3 -1	(R)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	2+2 days
C-peptide[f]	X																			
Safety Laboratory																				
Hematology[g], Clinical Chemistry[h]	X																			
Urine analysis[i]	X																			
Pregnancy test (WOCBP only)[j]	X		X				X				X				X				X	
AE / SAE	To be assessed and reported (if any) throughout the study (report SAE to the sponsor within 24 hours)																			
Injection site reactions, hypersensitivity reactions	To be assessed and reported (if any) throughout the study																			
Hypoglycemia recording	To be assessed and reported (if any) throughout the study																			

* additional screening visits may be needed for patients who cannot handle CGMS at home in order to generate 4 days of useable CGMS data prior to randomization.

a Telephone visit; Note: Telephone counseling will be available at any time as required.

b Or early termination visit. Patients who failed to provide 4 days of usable CGM data will be retrained and will repeat the blinded CGM course.

c Heart rate and blood pressure (sitting position)

d If a patient fails the first attempt for any reason, he/she will be retrained for CGM conduct and complete another course of blinded CGM.

e SMPG to be performed by trial patients after Visit 1 and throughout the study duration:

1. Fasting (prebreakfast/preinjection) SMPG: daily until dose optimization has been completed and fasting SMPG goal is reached. Thereafter, the number of fasting SMPG checks can be reduced according to the investigator's judgment, however at least 3 fasting (prebreakfast) SMPG measurements per week should be done.
   Note: after randomization, the pre-breakfast SMPG (including in 5-point and 7-point SMPG profiles) should follow the time window for Pre-injection plasma glucose
2. Pre-injection SMPG (within 30 min prior to injection of Toujeo or Lantus before breakfast) during the 16-week treatment period: at least on 5 days per week during the week prior to each on-site visit after randomization (Visit 7, 11, 15 and 19)) and the SMPG value must be assigned by the patient in the diary
3. 5-point SMPG profile (prebreakfast, prelunch, predinner and **2-hour post a main meal or follow the investigator's instruction and bedtime**): at least on 5 days per week throughout the study, starting after Visit 1**. Patients should test their 2-hour post meal SMPG after main meals (e.g. lunch or dinner) or follow the investigator's instructions for meal-time insulin titration.** Once the titration goal is reached (fasting and 2-hours postprandial SMPG stable in the target range), the number of 5-point SMPG profiles can be reduced according to the investigator's judgment but 5-point SMPG profiles at least on 3 days in the weeks that the5-point SMPG data are collected (section 10.2.3.2) are mandatory.
4. 7-point SMPG profile (before and 2 hours after breakfast, lunch and dinner, and bedtime): at least **ONE** day during the weeks prior to Visit 3, 15 and 19

f Only for patients without documented test results to assess the relevant exclusions

g Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes and platelets

h Clinical chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), AST, ALT, ALP, plasma glucose, creatinine, estimated creatinine clearance, uric acid, sodium, potassium

i Urine analysis: pH, glucose, ketones, leucocytes, blood/hemoglobin, protein

j For women of childbearing potential (WOCBP): serum pregnancy test for screening; urine pregnancy test for subsequent monitoring and if needed, it can be confirmed by a serum test.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferases
CGM:	continuous glucose monitoring
DBP:	diastolic blood pressure
DRF:	discrepancy resolution form
e-CRF:	electronic case report form
FPG:	fasting plasma glucose
GCP:	good clinical practice
GFR:	estimated glomerular filtration rate
HbA1c:	glycated hemoglobin A1c
HGLT:	high group level term
HLT:	high level term
ICH:	International Conference for Harmonisation
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
IVRS:	interactive voice response system
IWRS:	interactive web response system
LLT:	lower level term
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified Intent-to-Treat
NIMP:	non-investigational medicinal product
NPH:	neutral protamine Hagedorn
PT:	preferred term
PTC:	product technical complaint
RR:	rate ratio
SBP:	systolic blood pressure
SC:	subcutaneous
SMPG:	self-monitoring plasma glucose
SOC:	system organ class
USPI:	United States package insert
WOCBP:	women of childbearing potential

4 INTRODUCTION AND RATIONALE

Insulin glargine (HOE901) is a recombinant analog of human insulin providing a 24-hour (h) basal insulin supply after a single-dose subcutaneous (SC) injection. Insulin glargine U100/mL formulation has been marketed as Lantus for 15 years (1). Its efficacy and safety are well-known through extensive data collection involving over 100 000 patients in clinical studies, including randomized, controlled clinical trials and the results of postmarketing surveillance arising from approximately 30 million patient-years of clinical experience.

HOE901-U300 has the same composition as the current Lantus formulation 100 U/mL with adjustment of 3-times the amount of active pharmaceutical ingredient (insulin glargine) and corresponding zinc content and is also approved as Toujeo for once daily injection (2).

Further information on Lantus and Toujeo, including important clinical trials performed pre and post-registration, can be found in the national product labels and Investigator´s Brochure HOE901 (3).

As evidenced in previous euglycemic clamp studies (PKD10086, PKD11627 and TDR11626) after a single dose or multiple doses in healthy subjects or patients with Type 1 diabetes (T1DM), there are differences between Lantus and Toujeo in Pharmacokinetics (PK) and Pharmacodynamics (PD) profiles (3). In those euglycemic clamp studies, Glargine -U300 (Gla-U300), as compared to glargine-U100 (Gla-U100), showed less variability to the average concentration, displayed a flatter PK profile, and correspondingly less fluctuation in the glucose lowering activity. Given these features of the PK/PD profiles, Toujeo is considered to be well suitable for constant, peak less 24-hour basal insulin supply in diabetes management, with the expectation of less hypoglycemic risk at equal to tighter blood glucose control.

Clinical implication of Toujeo in management of type 1 diabetes was investigated in clinical studies in patients with T1DM. The EDITION-4 phase 3 trial in patients with T1DM showed similar therapeutic efficacy between Gla-300 and Gla-100 with respect to glucose lowering, while a slightly lower risk of hypoglycemia was observed for Gla-300 (4). PDY12777 was a small-scale (59 patients divided into 4-treatment arms) exploratory study using continuous glucose monitoring system (CGM), which provided sufficient data for diurnal glucose patterns associated with Gla-U300 or Gla-U100 treatment. CGM analysis in participants with T1DM showed better glucose stability and lower intra-patient glucose variability with Gla-U300 than Gla-100. These differences were more evident with the morning injection regimen. Moreover, the incidence of confirmed or severe hypoglycemic events was numerically lower with Gla-300 than with Gla-100. However, neither of the two studies was sufficiently powered to demonstrate reduced rates of hypoglycemia with Gla-300.

The present study LPS14587 is designed to further explore differences between Toujeo and Lantus with the hypothesis that Toujeo, compared to Lantus, given as the basal insulin to patients with T1DM will provide a better continuous glucose profile with less, in particular nocturnal hypoglycemia while the conventional glycemic control as measured by HbA1c is anticipated to be similar between the two treatments.

This is a randomized, active-controlled, 16-week open-label study to compare the efficacy of Toujeo with Lantus using CGM glucose profiles, sampling ambulatory glucose level every 5-minutes over at least 7 days at baseline and at endpoint (Week 15 or 16). CGM during screening and end of study period (Week 15 or 16) will be blinded to both the investigators and patients.

Eligible patients will be randomized to either Toujeo or Lantus, both given once-daily by subcutaneous (sc) injection in the morning. Patients will be required to titrate their basal and meal-time insulin to achieve the fasting and 2-hours post-prandial SMPG targets during the first 15 weeks of treatment. The CGM will then be performed during Week 15 or 16 during which period, basal insulin doses will be stable without changes.

The primary objective of the study is to demonstrate a greater percent of time in target CGM glucose range of 70-180 mg/dL with Toujeo than Lantus treatment. The main secondary objective is to evaluate the incidence and rate of hypoglycemia and possibly to show a lower rate of documented nocturnal symptomatic hypoglycemia with Toujeo versus Lantus. In addition, all hypoglycemia incidence and distribution (24 hours and nocturnal) will be analyzed according to the ADA classification (severe, documented symptomatic, asymptomatic, probable and relative) (5). Glucose stability and variability will be assessed between and within each group via measurements of diurnal glucose exposure, rate of change in median curve, interquartile range (IQR), mean and variation in glucose profiles, etc (6, 7).

A relatively homogenous patient population will be selected, reducing potential confounding effects, so that the true differences in the therapeutic effects of Toujeo versus Lantus can be assessed. The study population includes patients 18-70 years of age with T1DM, on a basal plus mealtime insulin regimen for at least 1 year, and glycated hemoglobin A1c (HbA1c) level >6.5 and < 10%. Lack of endogenous insulin production (C-peptide) is required to confirm type 1 diabetes (8). Patients must be on a stable dose of long-acting insulin analog basal/bolus regimen for 3 months before study entry. Furthermore, the number of prior hypoglycemia episodes is specified to include patients with known hypoglycemia that may benefit more from treatment with Toujeo.

Approximately 616 patients will be enrolled aiming for at least 524 (85%) evaluable patients, which will provide over 90% statistical power to demonstrate superiority with 4% margin of Toujeo over Lantus for the primary endpoint analysis. The 4% difference in the percentage of time glucose within the target range of 70-180 mg/dL is considered clinically relevant given the assumption that the HbA1c will be similar between the two treatments.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this Phase 4 clinical study is to demonstrate that morning injection of Toujeo compared to Lantus will provide better glycemic control evaluated by Continuous Glucose Monitoring (CGM) in adult patients with type 1 diabetes mellitus.

5.2 SECONDARY

The study is also aimed to demonstrate that treatment with Toujeo compared to Lantus will provide:

- lower incidence and rate of nocturnal symptomatic hypoglycemia
- better glucose control coverage during the last hours of CGM before next basal-insulin dosing
- less variability in CGM profile

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

LPS14587 is a multicenter, randomized, active-controlled, parallel group, 16-week open-label study. The study is a postmarketing Phase 4 trial which will recruit outpatients with type 1 diabetes mellitus who have been on basal plus mealtime insulin regimen for at least one year and currently taking a long-acting insulin analog (ie, Lantus, Toujeo, Levemir or Tresiba) plus rapid-acting insulin analogs to manage their diabetes.

This is a comparative study of Toujeo versus Lantus and the comparator is Lantus. The study has an open-label design, as the injection volume of the concentrated formulation of Toujeo (glargine-U300 is distinguishable from that of the Lantus (glargine-U100) formulation of insulin glargine.

The study will be conducted in the United States with approximately 100 participating sites. It's planned to recruit 616 patients in two parallel treatment groups:

- Toujeo group, n=308 patients
- Lantus group, n=308 patients

The study consists of an up to 4-week screening and CGM training period and a 16-week treatment period. Blinded CGM (blinded to both patients and investigators) will be conducted during the weeks of the end of screening (Week -2 to 0) and end of treatment (Week 15 to 16). The CGM data will be collected for efficacy analyses.

During the screening and baseline training period, patients will wear a blinded CGM device for 7 consecutive days to generate a minimum of 4 days of usable CGM data to be eligible for randomization. Patients satisfying the inclusion/exclusion criteria and CGM requirements will be randomized 1:1 to morning injection of either Toujeo or Lantus. The randomization will be stratified by baseline HbA1c (<8, ≥8), frequency of basal insulin injections BID vs QD at Visit 1, current CGM use (yes/no) at Visit 1 and mealtime insulin titration algorithm.

The protocol-mandated background therapy is mealtime insulin analogs, ie, rapid insulin analogs (eg, insulin glulisine, insulin lispro or insulin aspart), which has been used for at least 30 days before screening visit and which will be continued throughout the study. Any other glycemic lowering medications or other types of basal/bolus insulin are prohibited in this study.

Appropriate dose titration of basal and mealtime insulin will be conducted as specified in Section 8. Titration of basal insulin will be allowed until the end of week 14, after which, Toujeo/Lantus dose should remain unchanged during Week 15-16 for blinded CGM collection, while meal-time insulin dose can still be appropriately adjusted.

During the entire study starting after screening, patients will perform Self-Monitoring of Plasma Glucose (SMPG) which is specified in Section 1.2 and Section 10.2.3. SMPG readings will be

used to guide insulin dose-titration for optimal glycemic control and the SMPG profiles will be collected for study analyses.

During Week 15, patients will wear a blinded CGM device for 7 consecutive days to generate minimum 4 days of useable CGM data. If a patient fails the first attempt for any reason, he/she will be retrained for CGM conduct and complete another course of blinded CGM in Week 16.

At the end of the study, the patients will be followed-up for 2 (+2) days to collect post- treatment safety information.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study duration consists of:

- An up to 4-week screening and training period including 1-2-week CGM performance (allow for re-training). The screening starts from signed consent form.
- A 16-week open-label comparative treatment period, which includes 14 weeks of dose titration for both basal and meal-time insulin to achieve the glycemic targets and a 1-2 weeks of CGM performance when basal insulin (Toujeo and Lantus) doses are stable without changes.
- A 2-day (+2 d) post-treatment safety follow-up after treatment completion or premature discontinuation of study treatment.

For an individual patient, the maximum study duration is about 20 weeks.

6.2.2 Determination of end of clinical trial (all patients)

End of clinical trial is defined as the last patient completes the last visit (Visit 20).

6.3 INTERIM ANALYSIS

No interim analysis is planned for this study.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Adult patients (male and female) with type 1 diabetes mellitus;

I 02. Signed written informed consent

7.2 EXCLUSION CRITERIA

Patients who have met all the inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 4 sub-sections:

7.2.1 Exclusion criteria related to study methodology

E 01. Age <18 years or >70 years

E 02. Night shift worker,

E 03. Use of investigational drug(s) within 1 month or 5 half-lives, whichever is longer prior to screening,

E 04. Use of systemic glucocorticoids (excluding topical application or inhaled forms) for one week or more within 3 months prior to screening,

E 05. Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol (eg, acetaminophen/paracetamol during CGM period) and refusing to take alternative treatment,

E 06. Mental condition rendering the patient unable to understand the nature, scope and possible consequences of the study and to perform blood glucose monitoring requirements, including the documentation of SMPG data and insulin dosing, or evidence of an uncooperative attitude and/or inability to return for follow-up visits, and unlikely to complete the study,

E 07. Patients with severe unstable hepatic, gastrointestinal, cardiovascular (including congestive heart failure NYHA III/IV), respiratory, neurological, psychiatric, hematological, renal, endocrine, dermatological disease, active malignant tumor, other major systemic disease or patients with short life expectancy or any other medical condition that might interfere with the evaluation of study medication according to investigator’s medical judgment,

E 08. Hemoglobinopathy or hemolytic anemia, transfusion of blood or plasma products within 3 months prior to screening,

E 09. History of drug or alcohol abuse within 6 months prior to screening,

E 10. Pregnant or breast-feeding women or women who intend to become pregnant during the study period as glycemic control may be unstable and insulin doses may be variable during this period,

E 11. Patients unable to speak, read and write,

E 12. Patient is the Investigator or any subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

7.2.2 Exclusion criteria related to diabetes history and treatment

E 13. Patients with type 2 diabetes mellitus,

E 14. HbA1c ≤ 6.5% or ≥ 10% measured by the central lab test at Visit 1,

E 15. Patients with fasting c-peptide ≥ 0.3 nmol/l as per source document or central lab test at Visit 1,

E 16. Patients experienced none episode of documented symptomatic and/or severe hypoglycemia (as per the ADA classification) during the month prior to screening,

E 17. Patients experienced > 1 episode of severe hypoglycemia resulting in coma/seizures in the last 12 months before screening,

E 18. Patients receiving less than 1 year of treatment with basal plus mealtime insulin,

E 19. Using any basal insulins other than the long-acting insulin analogs (i.e. Lantus, Toujeo, Levemir or Tresiba) in the past 3 months before screening,

E 20. Requiring >80 U/day basal insulin analogs within 30 days prior to screening,

E 21. Not on stable dose of basal insulin analogs (20% total dose) within 30 days prior to screening,

E 22. Using human regular insulin as mealtime insulin within 30 days prior to screening,

E 23. Using less than 2 injections of rapid-acting insulin analog within 30 days prior to screening,

E 24. Using an insulin pump in the last 6 months before screening,

E 25. Initiation of any glucose-lowering agents in the last 3 months before screening,

E 26. Weight change of ≥5 kg in the last 3 months before screening.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 27. Any contraindication to use of insulin glargine as defined in the national product label,

E 28. End stage renal disease (creatinine clearance <15 mL/min or on renal replacement treatment),

E 29. Unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema likely to require laser, surgical treatment or injectable,

E 30. Women of childbearing potential (premenopausal, not surgically sterile for at least 3 months prior to the time of screening) not protected by highly-effective method(s) of birth control (as defined for contraception in the Informed Consent Form).

7.2.4 Additional exclusion criteria during or at the end of screening before randomization

E 31. Patient who has withdrawn consent before randomization (starting from signed informed consent form),

E 32. Inappropriate CGM use during screen period evidenced failure to obtain minimum 4 days of usable records by the end of screening,

E 33. Non-compliance with SMPG performance evidenced by failure to demonstrate at least 5 days of 5-point SMPG records by the end of screening,

E 34. Despite screening of the patient, enrollment/randomization is stopped at the study level.

E 35. Off-label use of any oral antidiabetic medication or non-insulin injectable agents during the 3 months prior to screening

Note: one time re-screening is allowed at the investigator's medical judgment for any manageable reasons that caused screening failure and the patient is likely to be eligible before the enrolment completes.

8 STUDY TREATMENTS

8.1 DIET AND EXERCISE

Diet and lifestyle counseling including training in carbohydrate counting, (if chosen to be used for the mealtime insulin titration) will be continued during the study. Dietary and lifestyle counseling should be given by a registered dietician or other medically qualified person (eg, diabetes educator, endocrinologist) and should be consistent with the recommendations of national or local guidelines (with regard to distribution of calories among carbohydrates, proteins, fats and to exercise) for individuals with type 1 diabetes.

Compliance with the diet and lifestyle recommendations will be discussed with the patients throughout the study, and more specifically in case of insufficient glucose control.

8.2 INVESTIGATIONAL MEDICINAL PRODUCT(S)

The IMP is insulin glargine (HOE901). It will be provided as either Toujeo (glargine U-300, the tested drug) or Lantus (glargine U-100, the comparator/control drug)

An instruction leaflet (Appendix B) will be provided which explains how to use the disposable pen-injectors for Toujeo. Patients will be trained or checked by study staff on how to use the pen correctly, how to store it and how to change the needle for both pen-injector devices.

8.2.1 Pharmaceutical formulation of the investigational medicinal product

The tested drug

Toujeo (insulin glargine 300 U/mL solution) is supplied for SC injection as a sterile, non-pyrogenic, clear, colorless solution in a 1.5 mL TOUJEO SoloStar disposable prefilled pen (450 U/1.5 mL).

Toujeo has the same composition as the Lantus formulation 100 U/mL with adjustment of 3-times the amount of active pharmaceutical ingredient (insulin glargine) and corresponding zinc content. The higher concentration of insulin glargine in U-300 will result for the **same dose of insulin glargine in lower injection volumes** as compared with the conventional U100 basal insulin formulations.

Application of the drug is done using the pen device allowing dose settings in the range of 1-80 U with 1U increments.

The control drug

Lantus is supplied as insulin glargine solution for SC injection 100 U/mL in 3 mL cartridges assembled in a pen-injector. The SoloStar prefilled (disposable) pen will be used and it allows for a dose setting in the range of 1-80 U with minimum dose increment of 1 U.

Note: Mixing of insulin glargine (either U-300 or U-100) with other insulins is not allowed nor dilution.

8.2.2 Route and method of IMP administration

Toujeo or Lantus, is self-administered once daily by deep subcutaneous injection, in the left or right anterolateral or left or right posterolateral abdominal wall or thighs or upper arms. The area of the injection will be consistent with the habits of the individual patient. Within a given area, location of the injection site of IMP should be changed (rotated) at each time to prevent injection site skin reactions. The area of the injection sites of IMP should be consistent throughout the study.

The injection sites for IMP and NIMP should be different so that, if any, an injection site reactions can be attributed specifically either to IMP (Toujeo or Lantus) or NIMP (mealtime insulin).

Patients will be provided with the pen injection devices specifically labeled for the use in the study.

The following pen needles will be provided for use with the injection pen devices:

- BD Ultra Fine Needles 31 G x 5 mm
- BD Ultra Fine Needles 31 G x 8 mm

Handling procedures of the pen and needles and administration technique is provided in specific manuals (see Appendix B). The patients are trained on the use of the study drug pen and needles by the study staff and provided with an instruction leaflet during the randomization visit (V3, Day 1).

For the duration of the study, the patients will be required to use the same type of study drug pens and needles.

Pen device issues (malfunctions) should be reported to the sponsor by the means of a procedure on product technical complaint (PTC) forms.

Injection pens should never be shared with others.

8.2.2.1 Toujeo (insulin glargine 300 U/mL solution)

Patients randomized to Toujeo (U300) will be supplied with the appropriate number of disposable pens for insulin glargine 300 U/mL and needles according to the dose range. Each pen contains a cartridge with a total 450 units of insulin glargine

Doses can be set in increments of 1 unit up to a maximum single injection of 80 U. Toujeo will be injected once daily in the morning throughout the study. Patients who require greater than 80 U per day in Lantus dose before the study will be excluded at screening. But during the study treatment period, if a dose greater than 80 units is required, it will be given as two or more consecutive subcutaneous injections **at the same time** with the daily dose split in equal or close to equal doses.

Splitting the doses into a morning and evening injection is not allowed.

8.2.2.2 Lantus (insulin glargine 100 U/mL solution)

Patients randomized to Lantus will be supplied with the appropriate number of disposable Lantus SoloStar pens and needles. Pens will be specifically labeled for the use in the study.

Each Lantus SoloStar pen contains a cartridge with a total of 300 units of insulin glargine. Doses can be set in increments of 1 U up to a maximum single injection of 80 U. Patients who require greater than 80 U per day in Lantus dose before the study will be excluded at screening. But during the study treatment period, if a dose greater than 80 units is required, it will be given as two or more consecutive subcutaneous injections **at the same time** with the daily dose split in equal or close to equal doses.

Splitting the doses into a morning and evening injection is not allowed.

8.2.3 Timing of IMP administration

Toujeo or Lantus will be injected once daily subcutaneously as randomized in the morning, which is defined as the time period between wakeup and breakfast. The injection will be always at the same time in the morning. The clock time of the once daily Toujeo or Lantus injection (hh:mm) in the morning is at the discretion of the patient and/or investigator. However, once that time is set, the IMP must be given within a ±1 hour window, which should be maintained for the duration of the study.

Treatment with the IMP will last until the end of treatment visit (Visit 19).

8.2.3.1 Changing injection time during screening period

Patients taking Lantus or other basal insulin analogs (i.e. Toujeo, Levemir or Tresiba) at anytime (eg, evening) other than in the morning should switch their injection time to the morning during the screening period after Visit 1. The instruction on changing injection time should be given by the investigator in concordance with the Lantus or other manufacture labels (1). On the day of switching injection time, the total dose of basal insulin analogs and the pre-breakfast (if applicable) rapid-action insulin may need to be reduced based on the physician's medical judgment.

For example, to change evening Lantus to morning injection:

On the day before changing injection time, the dose should be changed to ~ 1/2 - 2/3 of the total daily dose and will be injected in the evening as the patient's usual injection time.

On the second day the dose will be equal to the total daily basal insulin dose and injected in the morning before breakfast.

8.2.4 Starting dose of IMP

The starting dose of IMP at randomization is the patients' current Lantus or other basal insulin dose, ie, the dose on the day prior to Visit 3, for all patients who randomized to either Toujeo or Lantus.

The first injection of IMP should occur on the day of randomization (V3) under the supervision of investigator or the designated study staff. If for any reason, the patient could not inject the first dose at the study site, the first dose can be administered in the morning of the next day and the date and time will be documented in the eCRF for basal insulin.

8.2.5 Adjustment of IMP

After randomization, dose of Toujeo or Lantus will be titrated in dose steps outlined in Table 1 to achieve glycemic targets without hypoglycemia. The upward dose titration should continue until the patient reaches the target fasting (pre-breakfast/pre-injection) SMPG. ALL efforts should be made to reach the target ranges for plasma glucose by 6 to 8 weeks post randomization. Thereafter, the dose will be adjusted as necessary to maintain the glycemic control until the end of Week 14, after which, dose of Toujeo or Lantus should be **unchanged** during the CGM collection (Week 15 - 16) except in the case of dose reduction for safety reasons, eg, a basal insulin associated severe hypoglycemia.

The target range for fasting (pre-breakfast/pre-injection) plasma glucose is 80-100 mg/dL (4.4 and 5.6 mmol/L), inclusive.

As recommended in Table 1, changes in the Toujeo or Lantus dose are based on the average fasting pre-breakfast SMPG values of past 3 days measured by the patients. Other pre-prandial (pre-lunch, pre-dinner) SMPG measurements may also be taken into account.

If considered as helpful to achieve the fasting glycemic target by the investigator, the mealtime insulin (including bedtime) may be titrated before additional basal-insulin titration to achieve a bedtime and pre-breakfast glucose delta <50 mg/dL.

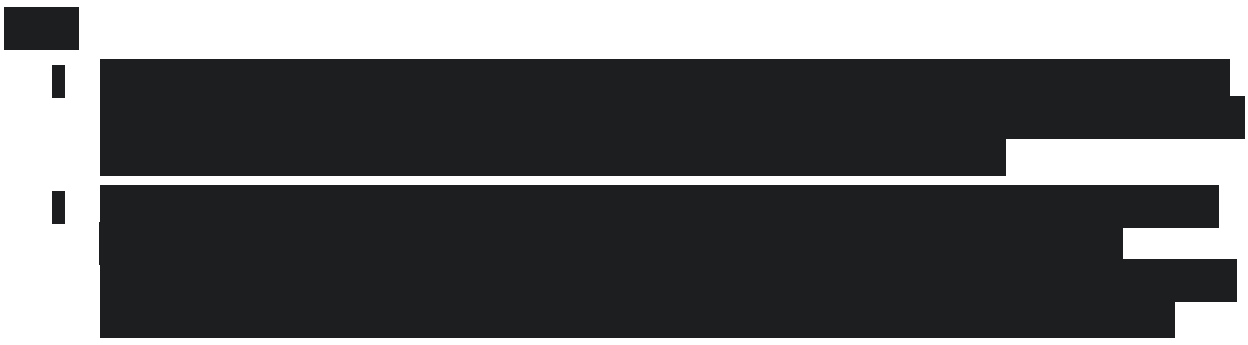


Table 1 - Titration of IMP dose

Mean fasting SMPG values (prebreakfast) from preceding 3 days	Insulin glargine (U-100 and U-300) dose adjustments (U/day)
>120 mg/dL (6.7 mmol/L)	+ 4 U, or split to 2 x 2 U
>100 and ≤120 mg/dL (5.6 and 6.7 mmol/L)	+ 2 U or split to 2 x 1 U
≥ 80 and ≤100 mg/dL (4.4 and 5.6 mmol/L)	No change
≥60 and <80 mg/dL (3.3 and 4.4 mmol/L)	- 2 U
<60 mg/dL (3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) documented in the preceding week.	- 2 to -4 U or at the discretion of the investigator or medically qualified designee

Good clinical judgment is to be exercised while titrating the basal insulin dose.

Regular self-monitoring of plasma glucose is very important in order to achieve the blood glucose targets. It is recommended to perform daily fasting/pre-breakfast SMPG and 5-point profiles (Section 10.2.3.1) to support the titration process. More frequent SMPG at other time-point (eg, post-breakfast and post-dinner) may be needed at the investigator's discretion.

Patients will be familiarized with the adjustment schedule so that they will be able to monitor the dose adjustment with the assistance of the investigator or medically qualified designee. During the study, weekly contacts between the investigator and patient are scheduled to assess the response to treatment and to decide on dose adjustment. During these visits (phone or onsite), patients will report their SMPG data, insulin doses and hypoglycemia to the study site.

If needed, additional contacts will be made available for patients to discuss dose adjustments in-between the scheduled visits. It is at the discretion of the investigator to allow well-trained patients to make their IMP insulin dose adjustments in between the scheduled visits without prior consultation of the site personnel.

Dose adjustment in cases of hypoglycemia:

- Upward titration is to be stopped for 1 week after a case of severe hypoglycemia (requiring assistance) or ≥ two episodes of documented symptomatic hypoglycemia within a week, unless there was a manageable factor (eg, omission of a meal or overdosed insulin) for the event,
- Doses of basal insulin or meal-time insulin may be reduced or modified at any time for hypoglycemia during the study,
- Small decreases of the insulin dose (eg, 1 unit) are at the discretion of the investigator or medically qualified designee, if SMPG is below 80 mg/dL (4.4 mmol/L) or if relevant hypoglycemia occurs,
- Patients who experienced mild to moderate hypoglycemia as a result of a missed meal, unusual exercise or alcohol use will be counseled on the correction of those behaviors and should not reduce their insulin dose.

8.2.6 Evaluation of patients not meeting glycemic targets

In case the target fasting glycemic goal cant not be achieved in spite of successive IMP dose titration over 4-8 weeks, the investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in fasting condition (eg, before breakfast within 30 minutes window prior to injection),
- IMP and mealtime insulin are properly injected,
- There is no inter-current disease which may jeopardize glycemic control (eg, infectious disease),
- Compliance to diet and lifestyle is appropriate,
- If any of the above can reasonably explain the insufficient glycemic control, the investigator should take appropriate action, eg:
  - Adjust the IMP dose and mealtime insulin dose,
  - Check the compliance of IMP and mealtime insulin injection,
  - Evaluate and treat intercurrent disease (to be reported in adverse event (AE)/serious adverse event (SAE)/concomitant medication parts of the e-CRF,
  - Organize a specific interview with a Registered Dietician or other medically qualified person to discuss with the patients on the absolute need to be compliant to diet and lifestyle recommendations.

8.3 NON-INVESTIGATIONAL MEDICINAL PRODUCT(S)

The non-investigational medicinal products (NIMP) are the protocol-mandated mealtime insulins, ie, rapid insulin analogs (insulin glulisine, insulin lispro or insulin aspart), which have been used by the patients since at least 30 days before the screening visit.

The patients in both treatment groups will continue with their existing mealtime insulin throughout the study. The type of mealtime rapid-insulin analog for each patient cannot be changed during the course of study. Any other types of meal-time insulin are prohibited for this study.

The injection sites should be different for the fast-acting mealtime insulin analogs from the IMP (insulin glargine) so that any injection site reactions can be attributed specifically either to the fast-acting insulin or to IMP. Changes in the body areas used for injection of either insulin should be avoided as far as possible during the study.

8.3.1 Adjustment of NIMP

The dose of the mealtime insulin analogs (glulisine, lispro or aspart) will be titrated to achieve a target of 2-hour postprandial plasma glucose. The dose adjustment regimen can be titrated based on a pattern of postprandial plasma glucose results of SMPG (simple titration) OR based on the carbohydrate content of the meal (carb counting).

- The **titration goal is a 2-hour postprandial SMPG in the range of 130 and 180 mg/dL (7.2-8.9 mmol/L)** while avoiding hypoglycemia. For the purpose of this protocol, 2-hour postprandial is defined as 2 hours after the start of the meal.
- While basal insulin doses are increased, mealtime insulin doses may be reduced to avoid daytime hypoglycemia as deemed appropriate by the investigator.
- Appropriate adjustment in mealtime insulin will continue throughout the entire treatment period (Week 0-16).

The two regimens are described in Table 2 and Table 3.

Table 2 - Simple titration: Titration of mealtime insulin based on a pattern of post-meal glucose (median 130</>180 mg/dL in the prior 3 days)

Mealtime dose of Insulin	Pattern of postprandial BG values <130 mg/dL[a]	Postprandial BG values >180 mg/dL[a]
≤10 U	Decrease dose by 1 U	Increase dose by 1 U
11-19 U	Decrease dose by 2 U	Increase dose by 2 U
≥20 U	Decrease dose by 3 U	Increase dose by 3 U

[a] If more than 50% of the mealtime blood glucose (2-hour PPG) values for the week were above target.

Table 3 - Carbohydrate counting: Insulin-to-carbohydrate ratio group

Mealtime dose of Insulin	Pattern of postprandial BG values <130 mg/dL[a]	Postprandial BG values >180 mg/dL[a]
1 U/20 g	Decrease to 1 U/25 g	Increase to 1 U/15 g
1 U/15 g	Decrease to 1 U/20 g	Increase to 1 U/10 g
1 U/10 g	Decrease to 1 U/15 g	Increase to 2 U/15 g
2 U/15 g	Decrease to 1 U/10 g	Increase to 3 U/15 g
3 U/15 g	Decrease to 2U/15 g	Increase to 4 U/15 g

[a] If more than one-half of the mealtime blood glucose values for the prior 3 days were above target.

Starting recommendation 1 U to 15 grams carbs

Consider calculating insulin to carb (I:C) ratio = 500 / total daily dose (TDD) of insulin.

Investigators will also be provided with an initial guideline of 1800/TDD as a correction factor to be used if applicable at the investigators' discretion.

The injection of the mealtime insulin analogs in relation to the meal intake will be done according to the individual habits of the patient prior to the study while following the instructions in the national product label.

Dietary modifications (eg, snacks) will be made by the Investigator, dietician or other medically qualified person based on his/her best judgment.

8.4 BLINDING PROCEDURES

As Toujeo and the control drug Lantus are distinguishable, this study is an open-label design. The day- time of injection is not blinded either. Administration of all forms of insulin glargine during the trial is to be open-label, and no attempt will be made to blind day-time of injection.

8.4.1 Compensation for lack of blinding

Despite the open-label administration of study insulins, assessment of outcomes, where possible, will be based on objectively collected data, which are assessments for blinded CGM (primary endpoint) and SMPG data. The SMPG data stored in the glucose meter will be uploaded to the site computer for the study staff to verify the diary entries that will be documented onto the eCRF to support the analyses of the 7-point SMPG profile and the confirmed hypoglycemia (secondary and other endpoints).

Neither the Investigator nor the Sponsor will have access to the individual data for the primary efficacy parameter (CGM records) obtained in each patient. However, the study team may review the data for the primary efficacy parameter in descriptive statistics with the name of the investigational medicinal product (IMP) treatment masked during data review meetings.

8.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The Trial Supply Chain Manager compiles the batch number list and the Study Biostatistician provides the randomization scheme (including stratification, Section 11) to the centralized treatment allocation system (IVRS - Interactive Voice Response System /IWRS - Interactive web response system). Then, the IVRS/IWRS generates the patient randomization list according to which it allocates treatment arms to the patients.

- The treatment kits, open-label boxes identified with batch numbers, are allocated to the patients by the IVRS/IWRS using the treatment number of the boxes.
- At the screening visit the investigator or designee has to call the IVRS/IWRS to receive 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).
- Randomization will be stratified by HbA1c obtained at the screening visit (<8.0%; ≥8.0%), Lantus (and other basal insulin analogs) injection at screening BID vs QD, current CGM use (yes/no) and mealtime insulin titration algorithm followed. For each region the IVRS/IWRS will be configured as to reach a minimum of 20% randomized patients per HbA1c strata.
- On V3 (D1), for first treatment kit(s) allocation, the investigator or designee has to call the IVRS/IWRS to provide some information (such as patient number provided by IVRS/IWRS at screening visit, date of birth, etc). Afterwards the IVRS/IWRS is called again each time a new treatment kit(s) allocation is necessary, ie, the visits as indicated in the study flowchart (Section 1.2).

- A randomized patient is a patient who has been allocated to a randomized treatment regardless whether the treatment kit was used or not (ie, patient registered by the IVRS/IWRS).
- A patient cannot be randomized more than once in the study.

8.6 PACKAGING AND LABELING

Toujeo (insulin glargine 300 U/mL solution) is supplied for SC injection as a sterile, non-pyrogenic, clear, colorless solution in a 1.5 mL Toujeo SoloStar disposable prefilled pen (450 Units/1.5 mL).

Lantus (Insulin glargine) 100 U/mL solution) is supplied as insulin glargine solution for SC injection 100 U/mL in 3 mL cartridges assembled in a pen-injector.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

The respective number of the study treatment will be packaged under the responsibility of sanofi according to good manufacturing practice and local regulatory requirement. Toujeo will be supplied in boxes of 3 disposable pens for insulin glargine 300 U/mL and Lantus will be supplied in boxes of 5 disposable pens for insulin glargine 100 U/mL

8.7 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing IMP in a secure and safe place in accordance with local regulations, labeling, specifications, policies and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

The expiry date is mentioned on the IMPs labels, and storage conditions are written on the IMPs labels and in the instruction leaflet.

8.8 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP 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 allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.8.1 Treatment accountability and compliance

At each contact to the patient, either by phone or during on-site visit, the Investigator or his/her delegate has to ask the patient about administered doses of IMP (Toujeo or Lantus).

Returned and dispensed IMP will be documented into the Treatment Log Form. Investigator or delegate has to visually check the filling status of the cartridges in the pens in the returned packs and compare to dosing records documented in the patients' diaries. Discrepancies have to be addressed to the patient for clarification of real treatment administration. For unused IMP, pens will have to be stored accordingly.

The investigator completes the appropriate treatment log form based on the unused, used and in-use IMP (study drug pens) returned and records the dosing information on the appropriate page(s) of the e-CRF. However as type 1 diabetes patients are requiring insulin, the level of glycaemia as reflected by SMPG and HbA1c is a sensitive marker of adherence to insulin treatment.

The monitor will check the e-CRF data by comparing them with patient's diary entries, treatment log forms and unused treatment kits.

8.8.2 Return and/or destruction of treatments

Patients have to return all the used, in-use and unused IMP at each on-site visit except for the visit where re-supply is not planned (at this visit, unused pen will be left home) (or final assessment on treatment visit in case of permanent premature discontinuation).

8.8.2.1 IMP (Toujeo or Lantus)

All partially-used or unused treatments (inject devices with inserted cartridges; disposable Solostar pens) will be retrieved by the Sponsor. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

The Investigator will not destroy any IMP unless the Sponsor provides written authorization. A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

A potential defect in the quality of IMP may initiate 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.

8.8.2.2 NIMP (mealtime insulin analogs)

As the mealtime insulin is not provided by the study sponsor, no NIMP return and destruction are required.

Patients have to record the administration of their mealtime insulin analog in the diary. ALL doses of mealtime insulin analogs during the day as taken for all meals and all snacks must be recorded. The sites have also to take care of source document of the NIMP in patient source documents and eCRF (NIMP name, dosage, daily total dose, injection compliance and dose-titration recommendation etc.) as specified in this protocol (Section 8.3).

8.9 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to IMP treatment. Any treatment which are continued during the study and/or initiated or changed during the study must be recorded in source data and in the e-CRF.

The IMP includes basal insulin of Toujeo and Lantus as the testing and control medications, respectively. Mealtime insulin analogs (glulisine, lispro or aspart) are the study required concomitant antidiabetic medication, which is defined as the NIMP in this study.

8.9.1 Prohibited medication during the study

During the study following medications are prohibited.

- Any antidiabetic agents other than the study medications mentioned above, including oral or injectable antihyperglycemic agents, other type of basal insulin (eg, NPH, Detemir, pre-mixed insulin), and human regular insulin,
- Insulin pump therapy is not allowed during the course of the study,
- Initiation of any weight loss drugs is not allowed; previous treatment with weight loss drugs can be continued and doses must remain stable throughout the study,
- Systemic glucocorticoids for more than 10 consecutive days (topical or inhaled applications are allowed),
- Medications containing acetaminophen/paracetamol **during the period of CGM** performance as these medications can interact with the glucose sensor of the CGM device.

Other medications which are unlikely to interfere with the IMP and the study variables are allowed as needed and discussed with the investigator. However, doses of chronically administered medicines should be kept fixed during the trial if at all possible.

8.10 POSTSTUDY TREATMENT

Upon discontinuation of the study treatment, either scheduled or early permanent discontinuation with IMP, patients may either continue with their basal insulin during the study, both available in the market, or take a treatment alternate, approved form of basal insulin.

The choice of the basal insulin used after the end of study and dosing instructions are at the discretion of the treating physician. After the transition to post-study basal insulin, the doses of the new post-study basal insulin and the short-acting mealtime insulin should be adjusted based on SMPG data and prescribing information. [redacted]

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary efficacy endpoint is the percentage (%) of time of glucose concentrations within the range of 70-180 mg/dL (3.9-10 mmol/L) during Week 15 (or 16), as obtained by CGM.

During Week 15, each patient will wear the CGM device for 7 consecutive days to generate at least 4 days of useable CGM records for the primary efficacy endpoint assessment. If a patient fails to provide at least 4 days (not necessarily consecutive) of useable CGM data over the 7-day CGM performance, he/she will repeat the CGM performance during Week 16.

- CGM data are blinded to both the patients and investigators,
- During the CGM performing week , the IMP insulin (Toujeo or Lantus) dose is fixed without a change, while the mealtime insulin dose can still be adjusted appropriately,
- Useable CGM data for a day are defined as at least 85% time of records without a gap (missing data) lasting for ≥ 2 hours per 24 hours. At least 4 days of qualified 24-h CGM records for each patient will be used for primary endpoint analyses,
- If a patient prematurely withdraws from the study before Week 15 (V18) the CGM data will be missing for the individual patient and the patient will be excluded from the primary efficacy analyses (see Section 11).

Further methods to handle missing data will be applied in the context of a sensitivity analysis and will be specified in the Statistical Analysis Plan (SAP).

9.2 SECONDARY ENDPOINTS

The secondary efficacy endpoints include:

- Incidence and rate of nocturnal symptomatic hypoglycemia, defined as an event with typical symptoms of hypoglycemia accompanied by SMPG ≤70 mg/dL (3.9 mmol/L) that occurs between 00:00 and 05.59 hours,
- Percentage (%) of time glucose concentrations obtained by CGM within target range of 70-140 mg/dL (3.9–7.8 mmol/L) during the last 4 hours of CGM data collection prior to next day basal insulin injection,
- Total, within day and between day coefficient of variation in glucose values obtained from CGM.

9.3 OTHER EFFICACY ENDPOINTS

- Frequency and distribution (nocturnal or 24 hours) of all hypoglycemia events analyzed by hypoglycemia categories (severe, documented symptomatic, asymptomatic, probable and relative) as defined in the publication ADA Workgroup on Hypoglycemia, 2015 (5),
- Additional CGM Endpoints (data obtained at Week 15 or 16) **:**
  - Percentage (%) of time glucose concentrations within the target range of 70-140 mg/dL (3.9–7.8 mmol/L), analyses on all- time (24 h) CGM data,
  - Percentage (%) of time glucose concentrations ≤70 mg/dL (3.9 mmol/L) and <54 mg/dL (3 mmol/L), analyses on both all-time (24h) and nocturnal (00:00-05:59 h) CGM data,
  - Percentage (%) of time glucose >140 mg/dL (7.8 mmol/L), >180 mg/dL(10 mmol/L) and > 250 mg/dL (13.9 mmol/L), analyses on both all-time (24h) and nocturnal (00:00–05:59 h) CGM data,
  - Total, within day and between day coefficient of variation in glucose concentrations,
  - Area under the glucose curve (AUC) of glucose concentration ≤70 mg/dL (3.9 mmol/L),
  - AUC of glucose concentration >180 mg/dL (10 mmol/L),
- 7-point SMPG profiles (pre-prandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, and bedtime),
- Change from baseline to study endpoint in HbA1c,
- Change from baseline to treatment period endpoint in central lab FPG,
- Insulin dose (total, basal, mealtime/bolus, ratio of basal to bolus insulin dose).

9.3.1 Hypoglycemia

9.3.1.1 Hypoglycemia classification

Hypoglycemia events will be categorized [5] as follows:

- **Severe hypoglycemia**

Severe 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 "requiring assistance of another person" means that the patient could not help himself or herself to treat the hypoglycemia. Assisting a patient out of kindness, when assistance is not required, should not be considered a "requires assistance" incident.

Any hypoglycemic event which leads to unconsciousness, coma, or seizure must be reported as an SAE. In addition, any hypoglycemic event, which at Investigator discretion, qualifies as serious adverse event must also be reported as an SAE.

- **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).

In addition, hypoglycemia episodes with plasma glucose of < 54 mg/dL (3.0 mmol/L) will also be analyzed.

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).

In addition, hypoglycemia episodes with plasma glucose of < 54 mg/dL (3.0 mmol/L) will be analyzed.

- **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**

Relative 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).

9.3.1.2 Hypoglycemia analyses

All hypoglycemia by above classification will be analyzed and presented as incidence rate per patient year and proportion (%) of patients with at least one hypoglycemic episode.

Hypoglycemia episodes will also be analyzed by their diurnal distribution (0:00-24:00) and in addition 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
- daytime hypoglycemia: any hypoglycemia of the above categories that occurs between 6:00 AM to 23:59.

The rate ratio (RR) of hypoglycemia of Toujeo versus Lantus will be assessed. Analytic methodology will be specified in Section 11 Statistic Consideration and the SAP.

9.3.2 Safety endpoints

Adverse events (AEs) spontaneously reported by the patient or observed by the Investigator, will be monitored.

The following safety parameters will be analyzed in this study:

- Adverse events, serious adverse events including injection site and hypersensitivity reactions
- Vital signs, including body weight
- Hypoglycemia

9.3.2.1 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 Group Level 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. The occurrence of AEs and SAEs is recorded from the time of signed informed consent until the end of the study.

If an AE/SAE is ongoing and not resolved by the end of the study observation period (defined as the time from randomization until the end of the study, Section 6.2.1) and leads to subsequent death of the patient, it will have to be reported.

9.3.2.2 Vital signs

Vital signs include:

Vital signs include: sitting blood pressure, and pulse measurements which will be recorded with the patient in a sitting position for 5 minutes before the measurement is taken.

9.4 FUTURE USE OF SAMPLES

Not applicable

9.5 APPROPRIATENESS OF MEASUREMENTS

The primary efficacy analysis will test superiority of Toujeo compared to Lantus in terms of percentage of time CGM data in the range 70-180 mg/dL (3.9-10 mmol/L). The tested CGM will be collected during the last week of IMP treatment with stable doses (unchanged dose) for either Toujeo or Lantus. Continuous glucose monitoring system allows frequent glucose measurements (every 5 min) and the ability to analyze glucose distributions in real time (9). Use of this approach in a clinical study provides the opportunity to better understand glucose metabolism associated with the study IMP. This approach has been employed previously in studies of the efficacy of long-acting insulins in patients with diabetes.

The 15-week treatment is considered sufficient for Toujeo, in the first 1-2 weeks, to achieve the steady state conditions after changing over from Lantus in a stable dose (< 20% +/-) prior to the study entry and for both Toujeo and Lantus to reach the optimal dose by following fasting SMPG-orientated dose titration regimen during the rest of treatment weeks. Mealtime insulin titration will also be implemented to achieve the postprandial SMPG targets. Thus, the glycemic control measured by laboratory HbA1c and FPG at the end of treatment is expected to be similar between the two treatments.

Secondary analyses will be performed to evaluate the therapeutic feature of a flatter and longer duration of Toujeo compared to Lantus over at least 24 hours, which should result in more sustained glycemic control, especially during the last a few hours before the next injection, and less hypoglycemia during nighttime. The assessment will be measured by the secondary endpoints of: the incidence rate of nocturnal documented symptomatic hypoglycemia, the percentage of time CGM in the target range during the last 4 hours prior to injection and the variability analyses of CGM profiles.

The other efficacy endpoints include a thorough hypoglycemia analysis on incidence rate, proportion of patients with hypoglycemia and the diurnal distribution of hypoglycemia. The analyses will be performed based on the SMPG and the hypoglycemic events reported by the patients. Patients will be instructed to measure SMPG whenever they feel hypoglycemic. This aims to detect and confirm as many hypoglycemic episodes as possible.

Frequent SMPG will be performed throughout the entire study period after Visit 1 (Section 10.2.3 and Section 1.2). SMPG values will be used to guide the insulin dose titration and to support the analyses of 7-point SMPG profile and hypoglycemia reports. To ensure the accuracy of the glucose records, SMPG data will be uploaded from the glucose meter onto the site computer via the [redacted] at each onsite visit so that the investigator and study staff are able to verify the glucose values documented by the patients in the study diary.

10 STUDY PROCEDURES

This is an approximately 20-week outpatient study and consists of 8 onsite visits and 12 mandatory telephone visits. Additional, optional telephone visits to monitor and support the progress of insulin titration should be scheduled whenever considered necessary by the investigator. Two repeated onsite visits at the end of screening and/or study treatment may be scheduled for patients who fail the first attempt of CGM performance.

All onsite visits should take place in the morning at approximately the same time. On the day before each onsite visit, patients should be reminded to bring the medical devices (glucose meter and/or CGM), diaries and IMP (used, in-use or unused) to sites and to be in the fasted status if required at some visits.

For phone-call visits, the patient is called by the investigator or qualified designee at a scheduled time.

A visit window of ± 3 days using the day of Visit 3 as reference is acceptable.

If one visit date is changed, the next visit should take place according to the original schedule, ie, counting from Day 1 on Visit 3.

For a complete list of procedures scheduled for each study visit please refer to the Study flowchart (Section 1.2). The aim of the following sections is to provide details on how some of the procedures have to be performed.

10.1 VISIT SCHEDULE

This paragraph describes how the visits are carried out, in chronological order (according to the flow chart and identical to the order shown in the CRF).

10.1.1 Screening and training Visits (Visit 1 and Visit 2)

The duration of screening and training period will be up to 4 weeks. Screening and training procedures will be carried out at Visit 1 and Visit 2, and completed at Visit 3. For a complete list of procedures scheduled for each study visit please refer to the study flow chart (Section 1.2).

As soon as a **patient is found ineligible**, the patient must not enter the randomized treatment phase and **IVRS/IWRS** has to be contacted in order to register the patient as a screening failure.

Patients can be re-screened one time before randomization in case of non-evaluable exclusion criteria (eg, not evaluable screening laboratory findings) or in case of manageable exclusion as deemed by the investigator. Re-screened patients will be subject to the screening visit procedures/assessments (see below) including new informed consent signed and allocation of a new patient number.

10.1.1.1 Visit 1 (Week -4)

Written informed consent must be obtained from the patient prior to any study-specific procedures. The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration and will be provided with the written information. In particular, blinded CGM will be specified in the consent form for patient to make an informed decision.

Collection of diabetes history will include documentation of duration of diabetes, history of microvascular [eye, kidney] and of neuropathic complications and their treatments. For patients with a documented medical history of proliferative retinopathy or macular edema, if the latest ophthalmologic investigation have been performed longer than 12 months prior to the planned randomization, the **patient has to be referred to an ophthalmologist** (or optometrist) **prior to randomization**. The previous experience with hypoglycemia during the past 12 months will be verified with the source document (Section 7.2). The source documents include (but not limited to) a physician's note, hospital/ER discharge note, printouts of glucose meter (or electronic data) or documents in the patient's diary.

Medical/surgical history may include macrovascular complications [heart, brain, legs] as well as all non-diabetic diseases. **Alcohol and smoking habits** are to be recorded.

Check of concomitant medication refers to documentation of medication including over-the-counter medication taken/administered within the previous 3 months prior to this visit.

Basal insulin analogs and mealtime insulin doses have to be recorded. If the patients have been on Lantus or other basal insulin analogs twice a day and or at other injection time than morning injection, **the investigator will instruct the patients to switch their basal insulin analog to once daily morning injection regimen**.

In women of child-bearing potential (WOCBP), the contraceptive methods, if used, have to be documented. According to CPMP/ICH/286/95 (10), "Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly."

A **physical examination**, including a **screening for diabetic neuropathy** (eg such as assessment of appearance of feet, ankle, reflexes, vibration perception at the great toes) has to be performed. Check for injection site reactions.

Blood will be drawn for all central laboratory tests needed for evaluation of the eligibility criteria (eg, HbA1c) of the patients. Patient has to provide a urine sample.

Patients will be **provided with appropriate study materials: blood glucose meter with corresponding supplies** (lancets, control solutions, test strips etc.). A control test will be completed and recorded to assure glucose meter accuracy. Patients will be shown how to accurately measure plasma glucose values with the blood glucose meter. CGM naïve patients should be introduced to CGM, eg, introducing DexCom CGM web portal.

A **patient diary** will be given to patients in order to perform self-measurement of plasma glucose and its recording. The **patient diary** further contains sections for the recording of time and dose of insulin injection, times of SMPG measurement, SMPG values, and hypoglycemia signs and symptoms. Patients should bring the used diary to each on-site visit, as it will be collected and exchanged by a new diary.

If needed, diet and life style counseling (including training in carbohydrate counting) should be provided.

IVRS/IWRS will be called for allocation of patient number (see Section 8.5), registration of screening, collection of demographic information.

10.1.1.2 Visit 2 (Week -3)

Visit 2 will occur about 1 week after Visit 1 when the investigator has received laboratory reports for the screened patients in order to assess Exclusion E14 and E15 (Section 7.2).

At this visit, patients will be trained with the blinded CGM performance. During the training the purpose of blinded CGM, the duration of CGM conduct, the requirement of daily calibration with SMPG and how to handle the device will be thoroughly explained and all questions be answered (Section 10.2.4). After the training, the patients will perform CGM sensor insertion under the supervision of the investigator or the study staff. Patients will stay at the study site for 2 more hours to complete the first calibration process and to receive additional training if needed. All patients will be instructed to wear the CGM device for 7 consecutive days.

Furthermore, following will be assessed:

- Changes from BID to QD Lantus injection and/or the injection time to morning injection from any other time (if applicable),
- Compliance with SMPG performance and at least 5 days of 5-point SMPG during the next week for randomization eligibility will be enforced. (Section 7.2.4),
- Any AE/SAE, including hypoglycemia since Visit 1 for eCRF documentation,
- Schedule for Visit 3 should include one day to perform the 7-point SMPG.

10.1.2 Randomization Visit (Visit 3, Day 1/Week 0)

Visit 3 will occur 7 days after Visit 2. If a patient is not able to keep the visit date for any reason, he/she should inform the study site immediately to reschedule the visit as soon as possible. In such a case, the CGM system will automatically stop working and the sensor/transmitter may be removed by the patient at home or at the site later (Section 10.2.4). Before the visit day, patients should be reminded to be fasted for about 8 hours and not to inject their Lantus at home in the morning of Visit 3 since the basal insulin (Toujeo or Lantus) will be injected at the site after randomization under the supervision of investigator or designees.

At this visit, quality of baseline CGM of each patient will be assessed to determine eligibility for randomization. Investigators will upload the CGM data via DexCom/ [redacted] and

review the CGM summary to determine the quality of CGM performance (Section 10.2.4.2). Study procedures at Visit 3 will also include SMPG data uploading, diary collection, AE/SAE including hypoglycemia, collection and 7-point SMPG collection.

Patients with qualified CGM records who do not meet any exclusion listed in Section 7.2.4 will proceed to randomization allocation. Patients will be provided with boxes containing prefilled pens for administration of IMP along with the instruction leaflet and corresponding supplies (needles, control solution, test strips etc.).

A patient card, including emergency contact details and treatment arm will be provided to every patient who participates in the study.

- Patients who are randomized to Toujeo will be instructed by the study staff on how to properly use the Toujeo pens (Appendix B),
- IMP administration will be explained to patients including communication of the IMP dose, time of the once daily administration and dose titration requirements (Section 8.2),
- The patients will inject their first IMP dose (Toujeo or Lantus) under the supervision of investigator or designee. The first injection dose is the patient's current Lantus dose, i.e., the dose injected in the morning before the day of Visit 3,
- Training on the correct usage of the blood glucose meter and patient diary will be repeated, if necessary.

All patients are asked to self-titrate their IMP (Toujeo or Lantus) according to the algorithm provided (Section 8.2.5). The short-acting insulin analog will be continued for mealtime insulin requirements and correction of SMPG according to recommendation (Section 8.3.1). Investigators and their study staff are required to offer adequate training, thus enabling patients to successfully self-titrate their insulins.

Patients who fail to provide at least 4 days of qualified CGM data will be retrained and will repeat the CGM performance for another week (Section 10.2.4.2). **Randomization will be delayed accordingly**.

For a complete list of procedures scheduled for each study visit please refer to the Study flowchart (Section 1.2).

10.1.3 Phone call Visits (V4-6, V8-10, V12-14 and V16-17)

During the study treatment period, 11 weekly phone call visits are scheduled between each on-site visit. The purpose of the weekly phone contact with the patients is to monitor the patients' compliance with SMPG and insulin titration and to collect injection information, AE/SAE, including hypoglycemia, as well as any change in concomitant medications.

Patient will be called by the investigator or qualified designee at a scheduled time. If the call has been completed by site staff other than the investigator, the investigator has to be consulted if AE/SAE is suspected. These visits are mandatory telephone visits, but can optionally be performed as onsite visits.

During the phone call the following points have to be addressed:

- Did you adjust IMP insulin since last visit? What are your actual IMP and mealtime insulin doses?
- Ask the patient about SMPG, and IMP and mealtime insulin doses during the last 7 days prior to the visits.
- Provide diet and life style counseling (including training in carbohydrate counting), if needed.
- Did you experience any new medical event, disease or symptom since the last visit? (Please pay attention to any possible hypoglycemic event or symptom, possible allergic or injection site reactions).
- Did you experience any change in a preexisting medical event or disease or symptom since the last visit?
- Did you change or add any concomitant medication since the last visit?
- Do you feel comfortable in handling the diary, glucose meter and IMP injection device or do you need any more explanation?

Further following procedures will be performed:

- Instruct patients on further insulin dose adjustment according to their SMPG values
- Remind the patients to measure required SMPG and complete the diary.
- Remind patients to perform the 7-point SMPG prior to Visit 15 and Visit 19
- Document change of concomitant medication and actual basal and mealtime insulin doses in the e-CRF.
- Report AE/SAE and hypoglycemia if any.
- Remind patients to be fasting prior to Visit 11 and Visit 19 and remind patient **not to inject** the IMP and/or breakfast mealtime insulin (if applicable) at home because the IMP will be injected at the study site after blood drawn for laboratory measurements.
- Remind patients to bring glucometer , diary and IMP (used, in use or unused) to each onsite visit.

For a complete list of procedures scheduled for each phone-call visit please refer to the Study flowchart (Section 1.2).

10.1.4 Onsite visits (V7, V11, V15 and V18) during treatment period

Four onsite study visits before the end of treatment are scheduled for dispensation of study material and IMP, SMPG data uploading and face-to-face discussion about the patients' progress, SMPG patterns, dose regimens and data collected during the study (eg, hypoglycemia, AE/SAE, average fasting and postprandial SMPGs over the past days).

Patients will bring their glucose meter, diary and IMP boxes to the study site at each visit.

The Investigators and study staff will check and **document in the source data, if the patient has reached the titration goal or not at each onsite visit**. Appropriate titration will be continued until target fasting SMPG without hypoglycemia has been reached.

SMPG data stored in the glucose meter will be uploaded to the study computer via [redacted] and the report will be available for the investigator to review and source document for tracking patients' SMPG performance and for the titration recommendation.

IMP compliance (collecting and counting used and unused cartridges and syringes and SMPG compliance (pre-injection SMPG, 5 point SMPG) will be checked and addressed with the patients.

Consultation for Diet and life-style modification should be provided during the onsite visits if needed.

Additional assessments will be performed at the specific visits:

- **Visit 11:** patients should be fasted and blood will be drawn for measurements of HbA1c and FPG at central laboratory,
- **Visit 15:** one day 7-point SMPG will be verified and data collected onto the eCRF,
- **Visit 18:** following will be performed:
  - Dispensation of CGM device and training for CGM conduct if needed,
  - CGM sensor insertion under the supervision of investigator or designees,
  - Patient will start wearing the blinded CGM device for 7 days,
  - The patients should be reminded that the IMP insulin (Toujeo or Lantus) dose should not be changed during the next week while the mealtime insulin dose can still be adjusted appropriately.

For a complete list of procedures scheduled for each study visit please refer to the Study flowchart (Section 1.2).

10.1.5 End of Treatment (EOT) visit (Visit19, Week 16)

End of Treatment visit (Visit 19) will occur 7 days after Visit 18 when the patients have completed the blinded CGM. If a patient is not able to keep the visit date for any reason, he/she should inform the study site immediately to reschedule the visit as soon as possible. In such a case, the CGM system will automatically stop working and the sensor/transmitter may be removed by the patient at home or at the site later (Section 10.2.4). Before the visit day, patients should be reminded to be fasted for about 8 hours and to bring the CGM device, glucose meter, study diary, used and all unused IMP to the sites. Patient should be reminded **not to inject** the IMP and/or breakfast mealtime insulin at home if applicable since the IMP will be injected at the study site.

At this visit, quality of CGM performance will be assessed before the end of treatment. Investigators will upload the CGM data via DexCom [redacted] and review the CGM summary to determine the quality of CGM performance (Section 10.2.4.2).

At this visit patients will inject the last dose of IMP which will be given after blood is drawn for laboratory measurements. In addition to all the performances done at each onsite visit, the EOT procedure will include CGM device collection, physical examination and vital signs and endpoint laboratory tests. SMPG will be uploaded, 7-point SMPG checked and all unused IMP collected.

Patients who fail to provide at least 4 days of qualified CGM data will be retrained and repeat the CGM for another week (Section 10.2.4.2). **End of treatment will be delayed accordingly**. All the procedures will be done or redone at the postponed EOT visit.

For a complete list of procedures scheduled for this study visit please refer to the Study flowchart (Section 1.2).

10.1.6 Follow-up Visit (Visit 20)

Following the last administration of IMP (Toujeo or Lantus) either as scheduled or prematurely, a posttreatment follow-up should be scheduled for all the patients in 2 (+2) days after permanent discontinuation of the study treatment. This visit can be a phone call visit, or an on-site visit in case of ongoing or new adverse event during the posttreatment period, if needed. The patient is called by the Investigator or qualified designee at scheduled time. If the call has not been performed by the Investigator, the Investigator has to be consulted if AE/SAE and hypoglycemic event are suspected.

During the phone call the same set of questions as listed for other telephone visits has to be asked (Section 10.1.3), except IMP related questions.

IWRS/IVRS has to be called in order to register end of study.

10.2 ASSESSMENT METHODS

10.2.1 Vital signs

Determination of the reference arm for blood pressure measurements: At visit 1 after the patient has rested comfortably for at least 10 minutes, blood pressure has to be measured on both of the patient´s arms while the patient is **in sitting position** and then again after two minutes on both arms. The arm with the higher diastolic blood pressure will be determined at this visit, identifying the reference arm for future measurement throughout the study. The highest value will be recorded in the e-CRF (all blood pressure values are to be recorded in the source data).

Blood pressure at all subsequent visits should be measured when the patient is quiet and seated and with their determined reference arm outstretched in line with mid-sternum and supported. Measurement at all subsequent visit should be taken under standardized conditions, approximately at the same time of the day, on the reference arm, with the same device (after the patient has rested comfortably for at least five minutes) and the values are to be recorded in the e-CRF. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be recorded. Devices for blood measurement should be regularly recalibrated according to manufacturers´ instructions.

Heart rate will be measured at the time of the blood pressure measurement.

10.2.2 Height and body weight

Height will be measured when patient´s shoes are off, feet together, and arms by the sides. Heels, buttocks and upper back should also be in contact with the wall when the measurement is made.

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer. The weight is read and recorded in the e-CRF and source data. Self-reported weights are not acceptable and patients must not read the scales themselves.

10.2.3 Self-monitoring blood glucose (SMPG)

Blood glucose values will be self-measured by the patients using the sponsor-provided **glucose meter** and corresponding supplies (lancet, control solutions, test strips etc). Patients should not use their own glucose meter during the study period starting after Visit 1.

10.2.3.1 SMPG performance

At Visit 1 patients will be shown how to accurately measure plasma glucose values with the blood glucose meter. The investigator or a member of the investigational staff will explain the need to measure glucose at the times requested for profiles and how to correctly record the values and times. Training is repeated as often as necessary at the study visits and the investigational staff reviews the patient's diary at each visit.

The performance of SMPG is outlined in Table 4 and also specified also in Section 1.2 Flow Chart.

Table 4 - Instruction for SMPG performed during the study

SMPG	Definition	Frequency		Prior to study visit
		Recommended	Mandatory	
Fasting (prebreakfast)	Within one hour prior to breakfast; after randomization, prebreakfast, = preinjection	Daily until achieving fasting SMPG target	Apply to preinjection SMPG	Apply to preinjection SMPG
Fasting Preinjection	within 30 min prior to injection of Toujeo or Lantus before breakfast	5 days per week	5 days during the week prior to each onsite visit	Visit 7, 11, 15, and 19
5-points	prebreakfast, prelunch, predinner + 2-hour post a main meal or as per investigator's instruction, and bedtime	5 days per week	3 days during the week prior to the visits that the SMPG data will be collected in the eCRF	Visits in Table 5

SMPG	Definition	Frequency		Prior to study visit
		Recommended	Mandatory	
7-points	before and 2 hours after breakfast, lunch and dinner, and bedtime	As needed	1 day during Week -1, 11, and 14	Visit 3, 15, and 19

SMPG readings will be used to guide the basal and mealtime insulin titration to reach glucose targets. The investigators should review the SMPG records at each onsite visit and also ask the pattern of fasting and postprandial SMPG at the phone visits so that they can provide instruction to the patients for appropriate insulin dose adjustment. Investigators may request more frequent blood glucose test and/or at specific time eg, midnight, if needed, to help the patients optimize insulin dosage.

Fasting SMPG

Before breakfast: will be measured daily until uptitration has been completed and fasting pre-breakfast SMPG is stable in the target range.

Note: After randomization, **before breakfast SMPG = Pre-injection SMPG**

Pre-injection SMPG: Within 30 min prior to injection of Toujeo or Lantus before breakfast: on the day of the first injection of the IMP (Day 1) and daily until uptitration has been completed and fasting pre-breakfast SMPG is stable in the target range, and then, at least 5 days per week before each onsite visit.

5-point SMPG profiles

Before breakfast (pre-injection after randomization), before lunch, before dinner and 2-hours post one of any meals and at bedtime (the post-meal SMPG may be done 2 hours after the patient's main meal, e.g. lunch or dinner, or as per investigator's instruction) at least 5 days per week during the week before the baseline until the fasting and postprandial glucose targets have been reached. However, it is mandatory to perform at least 3 days during the week prior to the visits that the SMPG data will be collected in the eCRF (Section 10.2.3.2).

7-point SMPG profiles

Before (pre-injection after randomization) and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner and at bedtime: at least one day in the week before the baseline visit and before Visit 15 and 19.

SMPG during symptomatic hypoglycemia

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 carbohydrate intake/administration of glucose whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate carbohydrate/glucose rescue prior to confirmation with the SMPG.

Patients have to document hypoglycemic events appropriately in their diaries and to contact the investigator as soon as possible following severe events for review and for decision on any necessary actions to be taken.

All hypoglycemia episodes will be documented on the "hypoglycemia specific form" in the e-CRF. This includes all symptomatic hypoglycemia events and asymptomatic hypoglycemia.

Hypoglycemia events fulfilling the criteria of a SAE will be documented on the SAE form in the e-CRF.

10.2.3.2 Recording SMPG data and insulin dose

Patients will document their SMPG values with the testing times in the sponsor-provided diary or an equivalent diary. When SMPG is recorded by the patient in a non-sponsor provided diary, the Investigator (or designee) and patient will sign/initial the data so that the dairy can be kept in the study source documents.

At each onsite visit starting at Visit 2, SMPG data stored in the individual's glucose meter will be uploaded via the [redacted] A summary including all measured glucose values will be promptly available for the Investigator (or designee) to review. For SMPG data to be captured in the eCRF, the investigators or study staffs must verify the accuracy with the data that are uploaded from the glucose meter. Once an error is identified, only the corrected data should be entered in the eCRF and erroneous data in the diary will be corrected by the patient and initialed.

Insulin dose and injection time for both basal insulin (Toujeo or Lantus) and mealtime insulin will be documented in the patients' diary on a **daily basis**. ALL doses of mealtime insulin analog during the day as taken for all meals and all snacks must be recorded.

Documentation of the SMPG and insulin dose in the corresponding e-CRF is specified in below table.

Table 5 - Documentation of SMPG and insulin dose in the e-CRF

Visit	3	4 ☎	5 ☎	6 ☎	7	8 ☎	9 ☎	10 ☎	11	12 ☎	13 ☎	14 ☎	15	16 ☎	17 ☎	18	19
Week	(R)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
5-point SMPG[a]		x	x	x	x	x	x		x		x		x		x		
7-point SMPG	x												x				x
SMPG hypoglycemia	Whenever documented in the patient diary associated with a hypoglycemic event																
Basal insulin dose (IMP)	X[b]	Daily dose as per the eCRF instruction															
Meal time insulin dose (NIMP)[c]	x	x	x	x	x	x	x		x		x		x		x		x

a 5-point SMPG profile: on 3 past days (not necessarily to be consecutive) during the week prior to these visits

b Baseline Lantus: total daily dose and injection time during the past 3 days prior to randomization

c Meal time insulin analogs: the total daily mealtime insulin dose and the number of injections (eg, ≤1, 2, 3 or >3) on 3 past days (not necessarily to be consecutive) during the week prior to these visits

10.2.4 Continuous glucose monitoring (CGM) related procedures

The CGM device to be used in the study is DexCom G4 Platinum professional (DexCom Inc., 6340 Sequence Drive, San Diego CA 92121 USA). All patients must use the CGM device provided by the sponsor during the blinded CGM collection periods. No personal CGM can be used during the weeks for the study specified CGM performance.

During the study, when the protocol required CGM is not performed (Week 1 through Week 14), patients who use CGM as a part of their routine diabetes management before the study entry are allowed to resume using their personal CGM. However, patients **cannot** initiate CGM system during the study if they have not applied the CGM as their glycemic monitoring regimen at the study entry, ie, the answer to the question of currently using CGM is "No" at Visit 1 (to be collected in the V1 eCRF).

10.2.4.1 CGM performance

Two sets of blinded CGM will be conducted by the study patients. Baseline CGM will start at Visit 2 and stop at randomization visit (Visit 3). The end-of-treatment CGM will start at Visit 18 and stop at the EOT visit (Visit 19). Patients must be well trained to understand the importance of the CGM performance and compliance of the manufacture (DexCom) instruction

All patients will undergo Webinar CGM training at Visit 2 (re-training as needed) provided by DexCom regardless previous experience with CGM. After the training, patients should understand the process of CGM and how to handle the CGM device at home, including daily calibration with SMPG, the distance of receiver and effect of temperature on the device etc. The CGM receiver's screen will be blocked of displaying data. Neither patients nor investigators will be able to see the glucose values.

Insertion of CGM sensor will occur at Visit 2 and Visit 18 under the supervision of the investigators or the designees. After the CGM sensor being implanted, the transmitter being attached, the patients will stay in the study site for 2 hours to perform one time calibration at the site. During the next 7 days when the patients are operating the CGM, they must:

- Calibrate the CGM with the SMPG twice a day, which can be done during the protocol specified SMPG performance (Section 10.2.3.1),
- Carry the CGM receiver with them all the time; the receiver must be placed within 20 feet (6 meters) from the patients' body in order to capture the data measured by the device.

Patients will receive a user guide of instruction included in the DexCom G4 Platinum Professional device kit. Technique support via a 24/7 help-line service for trouble shooting will be provided by the manufacture, DexCom. The patients should immediately contact the sites if they encounter any devise malfunction or device related events eg, sensor fracture. The investigator or a site staff will help patients contact the DexCom service line for problem solving.

10.2.4.2 CGM qualification and data transfer

After Visit 2 and Visit 18, each patient will wear the CGM for 7consecutive days to generate a minimum of 4 days (not necessarily to be consecutive) of usable CGM records. One day of qualified CGM data is defined as ≥85% recorded time over 24 hours without a gap lasting for ≥2 hours.

Next visits (Visit 3 and Visit 19) will occur after 7 days of CGM performance. If a patient cannot come for the site visit as scheduled he/she should inform the site immediately, as the CGM device will be automatically turned off. The patient may remove the sensor/transmitter by themselves at home or keep the "expired sensor" in place and remove it later during the site visit. Patients must bring the CGM device to the site at Visit 3 and Visit 19. The CGM will be uploaded into the study computer with [redacted] and a report summary with daily CGM performance will be available immediately. Investigators will not be able to see the recorded glucose values, nor will the report include any real glucose data. The CGM summary will be used for the investigators to review the patient's daily performances and determine the quality of CGM.

Investigators must review and print out the [redacted] summary (to be source documents). One day of CGM record is considered as qualified and useable if it meets follows:

- the daily performance hours are marked as 24 hours ie, a record of <24 hours does not count for a day
- the percentage of captured records is ≥85% of time (calculated by the system) over 24 hours
- during the 24 hours of a day, there is no gap (missing records) lasting for ≥2 hours

Only patients with 4 days of above qualified CGM records that are indicated in the [redacted] CGM report will proceed to randomization or end-of-treatment. If for any reason, a patient fails to complete the qualified CGM, he/she will repeat the course of CGM. In such a case, all efforts should be made to help the patient find the root-cause of the failure and succeed in the next attempt.

In such a case, completion of procedures at Visit 3 for randomization or Visit 19 for the end of treatment will be postponed.

10.2.5 Laboratory

Blood sampling for central laboratory assessments will be performed at 3 visits during the study (flow chart, Section 1.2). Urine samples will be collected at Visit 1.

- Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes, platelets);
- Clinical chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), AST, ALT, alkaline phosphatase (ALP), creatinine, estimated GFR, sodium, potassium;
- C-Peptide at Visit 1 only for those patients that a documented C-Peptide value is not available in the source document.
- Urine analysis (assayed by the central laboratory): pH, glucose, ketones, leucocytes, blood/hemoglobin, protein;
- Serum pregnancy test in women of childbearing potential (WOCBP) at screening and urine pregnancy test at most onsite visits will be performed. Urine pregnancy tests can be performed more often if needed and confirmed by a serum test if positive.

Note: Any abnormal laboratory value estimated as clinically significant by the investigator should be immediately rechecked (whenever possible using the central laboratory) for confirmation before making a decision of permanent discontinuation of IMP for the concerned patient. Any confirmed laboratory abnormality estimated as clinically significant by the investigator must be reported as an AE/SAE as applicable.

10.3 DEFINITION OF SOURCE DATA

10.3.1 Source data to be found in patient´s file

All 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,
- Study identification (name),
- Patient number, Confirmation of randomization, Treatment batch number (treatment arm), dates and doses of study medication administration,
- Medical, surgical, diabetes history, including information on:

  - Demography, inclusion and exclusion criteria,
  - last participation in a clinical trial,
  - Contraception method for women of childbearing potential (WOCBP),
  - Previous and concomitant medication,
- Dates and times of visits and assessments including examination results (Vital signs, height, body weight, laboratory reports),
- The printouts of CGM performance summary that are provided by [redacted] for both the baseline and EOT weeks,
- Printouts of uploaded SMPG that will be available via [redacted] at each onsite visit,
- Insulin dose (both basal and mealtime) titration assessment and recommendation for insulin dose adjustment,
- Investigator/Physician notes, Nursing notes, Dietician's notes,
- 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.
- Patient diaries.

10.3.2 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.

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.4.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator or the attending physician(s) for adverse events (eg, treated with IV insulin). Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the

responsibility of the IMP in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.2).

Patients will have to document any temporary discontinuation of the IMP insulin in the diary (date/time of last injection of the IMP insulin; date/time of resuming IMP insulin injection). 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 e-CRF pages when considered as confirmed.

Temporary treatment discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the patient.

10.4.2 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.

10.4.3 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 document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Criteria for permanent treatment continuation include:

- At the patient’s own request, eg, withdrawal of consent for treatment
- If, in the investigator's opinion, continuation with the administration of the study treatment would be detrimental to the patient's well-being, (eg, requiring treatment with insulin pump)
- Pregnancy
- Specific request of the sponsor.

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

10.4.4 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, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

After permanent discontinuation of the IMP, patients will return to standard of care based on investigator and patient healthcare providers' clinical recommendation.

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

10.4.5 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. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. If possible, the patients should return for an onsite visit and assessed using the procedure planned for the end-of-study visit (Visit 19).

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter)

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

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

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Definitions of adverse events

10.5.1.1 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.

10.5.1.2 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 (seizures, 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.

10.5.1.3 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.

List of AESI:

- 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 10.5.1.2),
  - 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 nonserious) with IMP/NIMP,
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic IMP count) and resulting in clinical symptoms and/or signs and considered a "significant overdose" by the Investigator,
  - Of note, asymptomatic overdose has to be reported as a standard AE,

10.5.2 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.
- 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).
- 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

10.5.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees 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.

10.5.4 Guidelines for reporting adverse events of special interest

10.5.4.1 Reporting of adverse events of special interest with immediate notification

ENTER (within 24 hours) the information related to the AESI in the appropriate AESI form of the e-CRF.

For AESIs with immediate notification, the AESI support documentation will be faxed to Quintiles Lifecycle Safety within 1 working day, even if not fulfilling a seriousness criterion, using the e-CRF.

Pregnancy :

- Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria,
- In the event of pregnancy, IMP should be discontinued,
- Follow-up of the pregnancy is mandatory until the outcome has been determined,

- Symptomatic overdose with IMP/NIMP :
  - An 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.

10.5.4.2 Reporting of adverse events of special interest without immediate notification

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 (not based on accountability assessment). It will be recorded as an AE “Asymptomatic Overdose (accidental or intentional)”.

10.6 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 health authorities, IECs/IRBs as appropriate and to the Investigators,
- all SAEs that are expected and at least reasonably related to the IMPs to the health authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected [please refer to the “Adverse Reaction section” in the United States Package Insert (USPI) for Lantus ((1) and Toujeo (2)].

Any other AE not listed in the "Adverse Reaction" in the USPI will be considered as unexpected.

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

10.7 SAFETY INSTRUCTIONS

Safety instructions are provided for SMPG (see Section 10.2.3), CGM (see Section 10.2.4), Hypoglycemia (see Section 8.2.5 and Section 9.3.1), AE, SAE (see Section 10.5.1.2), Vital Signs (see Section 10.2.1), and Obligation of the investigator regarding safety reporting (see Section 10.5).

The Investigator is the primary person responsible for taking all clinically relevant decisions on safety issues.

If judged necessary, the opinion of a Specialist should be envisaged in a timely manner (eg, acute renal failure, convulsions, skin rashes, angioedema, cardiac arrest, electrocardiographic modifications, etc.).

10.8 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

The material in Section 11 of the clinical trial protocol constitutes the statistical analysis plan for the study. In case this plan needs revision during the study to accommodate clinical trial protocol amendments or to adapt to unexpected issues in study execution and data that affect planned analyses, a statistical analysis plan will be developed before first patient is enrolled and issued prior to database lock.

11.1 DETERMINATION OF SAMPLE SIZE

A sample size of 262 evaluable patients per treatment arm would provide at least 90% power to demonstrate superiority of Toujeo over Lantus for the primary efficacy variable of the percentage of time plasma glucose within the range of 70-180 mg/dL during Weeks 15-16 of the study. The calculations were based on a superiority hypothesis using a t-test at a 2-sided 5% significance level and assumes an absolute difference of at least 4% of time in range, a common standard deviation of 14% (assumed based on the prior AM data from the PDY12777 study), and an expected value of 53% in the Lantus arm. As a generalized linear model will be used for the primary analysis, the power should be somewhat higher due to reduced estimate variability versus the t-test.

Considering prior data from the AM arms of the PDY12777 and EDITION-4 studies, this sample size would also provide at least 80% power to demonstrate a difference in the key secondary endpoint of the rate of documented symptomatic nocturnal hypoglycemia occurring at any point post randomization, assuming a rate ratio (Toujeo over Lantus) of at most 0.86 events per pt-year. Testing of this key secondary endpoint will be considered informative if superiority of the primary endpoint is met.

Calculations were made using nQuery Advisor v6.01.

11.2 DISPOSITION OF PATIENTS

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

Randomized patients consist of all patients who have been allocated a treatment kit number as recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not. Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

The randomized population will include any patient who has bene allocated to a randomized treatment regardless of whether the treatment kit was used or not.

11.3.1 Efficacy populations

11.3.1.1 Modified intent-to-treat population

The efficacy analysis population will be the modified Intent-to-Treat (mITT) population, which will consist of all patients who are randomized and who have at least one post-baseline assessment of the endpoint of interest.

11.3.2 Safety population

The safety population will be comprised of all patients who take at least one dose of randomized treatment, and will be analyzed as-treated (according to the treatment actually received). In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than one study treatment during the trial, the treatment group allocation for as-treated analysis will be the treatment group in which he/she is treated for longer.

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, ignoring temporary drug discontinuation. It will be calculated as (Date of the last IMP administration – date of the first IMP administration) + 1. The exposure to IMP will be summarized categorically (counts and percentages) on the safety population. If appropriate, exposure will also be summarized by starting dose.

Also dose changes from baseline at the end of treatment for IMP (U and U/kg) will be summarized by starting dose groups for the safety population.

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. Overall treatment compliance is defined as the actual number of days with at least one administration of IMP compared to the planned number of days with IMP administration during the open-label treatment periods up to treatment discontinuation.

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance of <80% will be summarized. In addition, the number and percentage of patients with at least 1 above-planned dosing administration will be given, as well as the number and percentage of patients with 0, (0, 20%], and >20% under-planned dosing administrations. No imputation will be made for patients with missing or incomplete data.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

The percentage of time plasma glucose within target range of 70-180 mg/dL (3.9–10 mmol/L) during Weeks 15-16 (obtained from CGM) will be calculated based on the total time within glycemic range in the evaluable assessment interval, divided by the total time of the evaluable assessment interval.

The evaluable assessment interval for the calculation will comprise of 24-hour periods during Weeks 15-16 for which there is sufficient non-missing data. In order to be evaluable for analysis, a patient needs at least 4 days of 24-hour data meeting this criterion and should not receive protocol prohibited medication.

The endpoint will be summarized by treatment group using mean, median, standard deviation, minimum and maximum.

Differences between treatment groups will be explored using a generalized linear model, adjusting for key baseline characteristics (duration of diabetes, BMI, age and baseline value) and randomization strata. Adjusted mean estimates for each treatment with standard errors, the adjusted estimate of treatment mean difference with standard error and a 95 % confidence interval for the treatment mean difference will be provided. The statistical test will be for superiority of Toujeo over Lantus, two-sided and at a 5% significance level.

11.4.2.2 Analysis of secondary efficacy endpoint(s)

Nocturnal symptomatic hypoglycemia will be defined as an event with typical symptoms of hypoglycemia accompanied by SMPG ≤ 70 mg/dL (3.9 mmol/L) that occurs between 00:00 and

05:59 hours. The incidence will be analyzed using logistic regression, adjusting for randomization strata and other baseline characteristics (duration of diabetes, BMI and age) as clinically appropriate and if the model permits.

The rate per patient-year of nocturnal symptomatic hypoglycemic events will be analyzed using an over-dispersed Poisson regression model, adjusting for randomization strata and other baseline characteristics (duration of diabetes, BMI and age) as clinically appropriate and if the model permits.

The percentage of time glucose concentrations obtained by CGM within the target range of 70-140 mg/dL (3.9-7.8 mmol/L) during the last 4 hours of CGM data prior to the next day basal insulin injection will be calculated as the total time within that time period that the plasma glucose is in the range, divided by the length of that time period of observation.

The period of observation for the calculation will comprise of the last 4 hours during the final evaluable 24-hour period, where the evaluable period is defined as for the primary endpoint.

Total, within day and between day coefficient of variation (calculated for each period as the ratio of the standard deviation of the glucose values to mean of the glucose values).

Both the percentage of time glucose concentrations within the target range of 70-140 mg/dL (3.9-7.8 mmol/L) and the total, within day and between day coefficient of variation will be summarized at baseline and study endpoint by treatment group using mean, median, standard deviation, minimum and maximum, and will be analyzed as for the primary endpoint.

Other endpoints

The frequency and rates (nocturnal or 24 hours) of all hypoglycemic events will be analyzed for the hypoglycemia categories of severe, documented symptomatic, asymptomatic, probable and relative, as defined in the publication of the ADA Workgroup on Hypoglycemia, 2015. These hypoglycemia categories will be analyzed as for symptomatic hypoglycemia described previously.

The percentage of time plasma glucose in target range 70-140 mg/dL (3.9–7.8 mmol/L), and the percentage of time plasma glucose ≤70 mg/dL (3.9 mmol/L) and <54 mg/dL (3 mmol/L) will be calculated and analyzed as for the primary endpoint. For these endpoints, the time period of observation will be all evaluable time (24hours) and nocturnal, where nocturnal is defined as the period between 00:00-05:59 within the evaluable assessment interval.

The area under the curve (AUC) of glucose concentration ≤70 mg/dL (3.9 mmol/L) will be derived as the area above the CGM profile (ie, the median curve) and below this lower limit of the glycemia range, divided by the length of the evaluable assessment interval. The median curve will be obtained by superimposing the date-time-stamped glucose values collected by CGM into 24 nominal hourly baskets from which the point-wise median is calculated.

The AUC of glucose concentrations >180 mg/dL (10 mmol/L) will be derived as the area below the CGM profile (ie, the median curve) and above the upper limit of the glycemia range, divided by the length of the assessment interval. The median curve will be derived as defined previously.

All of the continuous CGM endpoints will be summarized, and will be analyzed using a generalized linear model as described for the primary endpoint.

The absolute values and change in 7-point SMPG profiles (pre-prandial and 2-hour post-prandial plasma glucose at breakfast, lunch and dinner, and bedtime) from baseline to Week 12, Week 16 and the last on-treatment value (study endpoint) will be presented descriptively by treatment group.

Summary statistics will also be presented for the absolute values and the change from baseline in HbA1c and central lab FPG to Week 8, Week 16 and last on-treatment value (study endpoint). The change from baseline to study endpoint will be analyzed using a mixed-effect model with repeated measures (MMRM) approach under the missing at random framework, using an adequate contrast at endpoint. The model will include fixed categorical effects of treatment arm, visit, treatment-by-visit interaction, randomization strata, and baseline HbA1c as covariate as well as baseline HbA1c-by-visit interaction.

Insulin dose (total daily dose (units, units/kg), basal, mealtime/bolus, ratio of basal to bolus insulin dose) will be descriptively summarized for absolute values and change from baseline.

11.4.2.3 Multiplicity considerations

Results of the secondary analyses are considered as informative only if the primary analysis is positive, and will be examined in a hierarchical step-down manner. Therefore the study overall type I error does not need to be adjusted for multiplicity.

11.4.3 Analyses of safety data

All safety and tolerance results will be presented by treatment group and on the safety population using the following common rule that the baseline value will be defined generally as the last available value prior to the first injection of IMP.

For all safety data, the observation period will be divided into three segments:

- The pre-treatment phase is defined as the time between when the patients give informed consent and time of the first IMP administration (excluded).
- The on-treatment phase is defined as the time from the first IMP administration (included) until 1 day after the last dose of IMP (until midnight of day after last IMP dosing day).

The post-treatment phase is defined as the time after the on-treatment phase until the end of treatment.

Adverse events

The primary focus of AE reporting is on TEAEs. Pre- and post-treatment AEs are described separately. If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm is used to classify the AE as pre-treatment, TEAE, or post-treatment. The algorithm for imputing date / time of onset is conservative and classifies an AE as

a treatment emergent unless there is definitive information to determine it is pre- or post-treatment.

The following TEAEs will be summarized: Overall TEAEs, serious TEAEs, TEAEs leading to death, TEAEs leading to permanent treatment discontinuation. TEAEs will also be summarized by relationship to study treatment, and by severity. All treatment emergent SAEs will also be presented separately.

Adverse event incidence tables will present the number and percentage of patients experiencing an AE by SOC, high level group term (HLGT), high level term HLT and preferred term (PT) sorted by internationally agreed order for SOC and in alphabetical order of HLGT, HLT and PT within a SOC for each treatment group. Multiple occurrences of the same event in the same patient is counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Injection site reactions and hypersensitivity reactions

The number and percentage of patients experiencing injection site reactions and hypersensitivity reactions will be summarized separately.

Death

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study, poststudy) and reasons for death (if available), summarized on the safety population by treatment received.
- Deaths in nonrandomized patients or randomized and not treated patients.

All TEAEs leading to death will be summarized by primary SOC, HLGT, HLT and PT, showing the number (%) of patients sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetic order.

Vital signs

Summary statistics for absolute values and changes from baseline of all vital signs variables, including body weight, will be calculated from the absolute values and changes from baseline for each visit or study assessment (baseline, each post baseline time point, last on-treatment during the on-treatment period of the study) by treatment.

The incidence of potentially clinically significant abnormalities (PCSA)s at any time during the on-treatment period will be separately summarized by treatment group whatever the baseline level.

11.5 INTERIM ANALYSIS

No interim analysis is planned.

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 subinvestigator, 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 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.

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.

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 released 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 at least annually and a summary of the clinical trial's outcome 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 subinvestigators shall be appointed and listed in a timely manner. The subinvestigators 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, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

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, documents and IMP 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 /subinvestigator 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 subinvestigators 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 subinvestigator, 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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8. Davis AK, DuBose SN, Haller MJ, Miller KM, DiMeglio LA, Bethin KE, et al. Prevalence of detectable C-Peptide according to age at diagnosis and duration of type 1 diabetes. Diabetes Care. 2015 Mar;38(3):476-81.

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