NCT04075513

CLINICAL TRIAL PROTOCOL

Protocol title:	**A 12-week randomized controlled trial to compare TOUJEO® and TRESIBA® in terms of glucose values in target range and variability during continuous glucose monitoring in patients with type 1 diabetes mellitus**
Protocol number:	**LPS14947**
Amendment number:	**Original protocol**
Compound number (INN/Trademark):	**HOE901-U300 (Insulin Glargine 300 U/mL/ Toujeo®)**
Short title:	**Comparison of glucose values and variability between TOUJEO and TRESIBA during continuous glucose monitoring in type 1 diabetes patients (inRange)**
Sponsor name:	
Legal registered address:	
Monitoring Team's Representative Name and Contact Information	

Regulatory agency identifying number(s):

EudraCT number:	2017-002756-91
IND number:	Not applicable
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NCT number:	Not applicable

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1.1 SYNOPSIS

Protocol title: A 12-week randomized controlled trial to compare TOUJEO® and TRESIBA® in terms of glucose values in target range and variability during continuous glucose monitoring in patients with type 1 diabetes mellitus

Short title: Comparison of glucose values and variability between TOUJEO and TRESIBA during continuous glucose monitoring in type 1 diabetes patients (inRange)

Rationale:

The fluctuations in blood glucose, regular short-duration periods of hyperglycemia and hypoglycemia, which are not detected by the measurements of glycated hemoglobin (HbA1c), may possibly contribute to vascular pathological processes and diabetic complications.

Insulin glargine U300 (HOE901-U300, Toujeo®) is a more concentrated formulation of insulin glargine U100 (HOE901) which showed a prolonged and flatter glucose-lowering activity (up to 36 hours) compared to Lantus (Insulin glargine U100), resulting in less circadian fluctuation in blood glucose levels (1). Given these features of the pharmacokinetic (PK)/pharmacodynamics (PD) profiles, Toujeo is considered to be well suitable for constant, peakless 24-hour basal insulin supply in diabetes management, with the expectation of less hypoglycemic risk at equal to tighter blood glucose control.

Tresiba® is a basal insulin that forms soluble multi-hexamers upon subcutaneous (SC) injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation leading to a flat and stable glucose-lowering-effect. This recombinant analog of human insulin provides basal insulin supply beyond 42 hours after injection in euglycemic clamp conditions in type 1 diabetes (2).

The present study LPS14947 is designed to further explore similarities and differences between Toujeo and Tresiba in terms of an effect on continuous glucose profile, while the conventional glycemic control as measured by HbA1c is anticipated to be similar between the 2 treatments.

Objectives and endpoints

Objectives	Endpoints
Primary	
To demonstrate the noninferiority of insulin glargine 300 U/mL in comparison to insulin degludec 100 U/mL on glycemic control and variability in participants with diabetes mellitus	Percent time in glucose range of ≥70 to ≤180 mg/dL (≥3.9 to ≤10 mmol/L) at Week 12, obtained using continuous glucose monitoring (CGM)

Secondary	
To evaluate the glycemic control and variability parameters in each treatment group at Week 12 using CGM	At Week 12, the following endpoints will be assessed: • Glucose total CV • Glucose within-day and between-day CV Other secondary endpoints: • Change from baseline to Week 12 in HbA1c • Change from baseline to Week 12 in central lab FPG • Percent time and mean hours per day with glucose<70mg/dL (on all time and during the night [00:00 to 05:59]) • Percent time and mean hours per day with glucose>180mg/dL
To evaluate the safety of insulin glargine 300 U/mL in comparison to insulin degludec 100 U/mL	Number of participants with adverse events (see Section 8.3) Number of participants with at least one hypoglycemic event from baseline to Week 12 Number of hypoglycemic events per participant year from baseline to Week 12

Overall design:

This is a multicenter, randomized, active-controlled, parallel-group, 12-week open-label study to compare the efficacy of Toujeo with Tresiba using 20-day CGM glucose profiles at Week 12. The CGM during study period will be blinded to both the Investigators and patients.

Study population will consist of participants with type 1 diabetes mellitus (T1DM), treated with multiple daily injections (MDI) using basal insulin once daily and rapid acting insulin analogs for at least one year, and having HbA1c ≥ 7% and ≤ 10% at screening (see full list of inclusion and exclusion criteria in Section 5).

Number of participants:

Approximately 338 patients will be randomly assigned to study intervention for an estimated total of 131 evaluable participants per intervention group (with the assumption of a non-evaluability rate of 22%).

Intervention groups and duration:

The study is planned to randomize 338 patients in 2 parallel treatment groups:

- Toujeo group, n=169 patients.
- Tresiba group, n=169 patients.

The duration of the study per patient will be around 18 weeks (1 or 2 weeks of screening followed by a 4-week run-in period, a 12-week treatment period and a 2 to 4 days follow-up period).

Study interventions

Investigational medicinal products

- Formulation:

  Test drug: Toujeo (insulin glargine 300 U/mL) is supplied as a sterile, non-pyrogenic, clear, colorless solution for SC injection in the Toujeo SoloStar prefilled, disposable pen. Each Toujeo SoloStar contains in total 450 units of insulin glargine (1.5 mL of 300 U/mL insulin glargine solution).

  Control drug: Tresiba is supplied as a sterile, non-pyrogenic, clear, colorless solution in the marketed Tresiba FlexTouch prefilled (disposable) pen (insulin degludec 100 U/mL solution for SC injection). Each Tresiba FlexTouch contains in total 300 units of insulin degludec (3.0 mL of 100 U/mL insulin degludec solutions).

- Route of administration: subcutaneous.
- Dose regimen: At randomization, patients will switch from their current basal insulin to either Toujeo or Tresiba in the morning. The initiation doses of Toujeo and Tresiba will be the patient's current doses of their basal-insulin analogs. During the titration phase (expected to be up to Week 8), doses of either Toujeo or Tresiba will be titrated to achieve glycemic targets without hypoglycemia. The dose will be titrated at least weekly (but no more often than every 3 days), until the patient reaches a target fasting SMPG of ≥70 to <100 mg/dL (≥3.9 to <5.6 mmol/L) while avoiding hypoglycemia episodes. Dose adjustments are based on a median of fasting SMPG values from the last 3 days, which includes the value measured on the day of titration, as measured by the patient using glucometers and accessories supplied by the Sponsor. Sponsor will ensure adequate monitoring of basal insulin titration.

Median[a] fasting pre-breakfast SMPG values (last 3 days)	**Basal insulin dose adjustments (U/day)[b]**
≥140 mg/dL (≥7.8 mmol/L)	+4 units
≥100 and <140 mg/dL (≥5.6 and <7.8 mmol/L)	+2 units
≥70 and <100 mg/dL (≥3.9 and <5.6 mmol/L)	No change
≥56 and <70 mg/dL (≥3.1 and <3.9 mmol/L)	-2 units
<56 mg/dL (<3.1 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode	-4 units or at the discretion of the Investigator or medically qualified designee

a Median refers to intermediate SMPG value (the value between the lowest and the highest SMPG values when the values are ranked in a growing order).

b Prior to additional basal insulin titration, mealtime insulin should be titrated to achieve a bedtime and pre-breakfast glucose delta <50 mg/dL, if so considered helpful by Investigator.

Noninvestigational medicinal products(s)

- Formulation: rapid-acting (mealtime) insulin analog (eg, insulin glulisine, insulin lispro or insulin aspart). The cost of the mealtime insulin analogue may be reimbursed if not covered by health insurance and if allowed by local regulations. Alternatively, the sponsor provided insulin glulisine may be offered.
- Route of administration: subcutaneous.
- Dose regimen: The injection time and frequency of rapid-acting (mealtime) insulin will be at the Investigator's discretion, in accordance with the National Product Label. During the study, the doses of the mealtime insulin analog should be actively titrated to achieve and maintain the 2 hour postprandial SMPG in the range ≥130 to ≤180 mg/dL (≥7.2 to <10 mmol/L) while avoiding hypoglycemia. 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. Sponsor will ensure adequate monitoring of mealtime insulin titration.

  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 Plasma Glucose values <130 mg/dL**[a]	**Postprandial Plasma Glucose 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 half of the mealtime plasma glucose (2-hours postprandial plasma glucose) 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 Plasma Glucose values <130 mg/dL**[a]	**Pattern of Postprandial Plasma Glucose 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 half of the mealtime plasma glucose values for the prior 3 days were above target.

Statistical considerations:

- **Sample size**

The sample size calculation is based on the percent time spent in glucose range of ≥70 to ≤180 mg/dL (≥3.9 to ≤10 mmol/L) at Week 12, assessed from CGM measurements obtained from Weeks 10 to 12.

For this criterion of percent time in range, there is no predefined non-inferiority margin. A relative non-inferiority margin of 10% is considered.

Let m1 and m0 be the true means for the Toujeo and Tresiba groups, respectively.

The non-inferiority null hypothesis would be H0: m1-m0 ≤ -0.1*m0 or H0: m1-0.9*m0 ≤0 and the alternative hypothesis (H1): m1=m0.

Toujeo would be considered non-inferior to Tresiba if the lower limit of the 95% confidence interval (CI) for the adjusted difference estimate of m1-0.9*m0 at Week 12 is > 0.

To ensure 90% power, the sample size should satisfy:

$$1.96 - \frac{(0.1 * m0)}{\sqrt{\frac{1.81 * SD^2}{n}}} = -1.282$$

Where -1.282 is the 10th percentile of a standard normal distribution and standard deviation (SD) the common SD.

which leads to: $n = \frac{(1.96+1.282)^2 * 1.81 * SD^2}{(0.1 * m0)^2}$

Assuming a common SD of 14.7%, an average percent time in range in the Tresiba treatment group of 56% (value from LPS14587), no true difference between both arms under H1, and a relative non-inferiority of 10%, a sample size of 131 evaluable patients per treatment group would provide at least 90% power to show non-inferiority of Toujeo with respect to Tresiba on the percentage of time plasma glucose within the range of ≥70 to ≤180 mg/dL at Week 12.

With the assumption of a non-evaluability rate of 22%, 338 patients (169 per treatment arm) will have to be randomized.

- **Primary analysis:**

The primary endpoint (percent time in glucose range of ≥70 to ≤180 mg/dL [≥3.9 to ≤10 mmol/L] at Week 12) using available data from the 12-week randomized period will be analyzed using an analysis of covariance (ANCOVA model including the fixed categorical effects of treatment group (Toujeo, Tresiba), randomization stratum of screening HbA1c (<8.0% versus ≥8.0%), as well as, the continuous fixed covariate of baseline percent time in range value. This procedure will provide baseline adjusted least-squares means estimates at Week 12 for both treatment groups, as well as, the differences of these estimates, with their corresponding standard errors (SEs) and 95% CI.

To assess non-inferiority, the lower bound of the two-sided 95% CI for the adjusted difference estimate of m1 - 0.9*m0 at Week 12 will be compared to 0.

Non-inferiority will be demonstrated if the lower bound of the two-sided 95% CI of the adjusted difference estimate of m1 - 0.9*m0 at Week 12 on the intent to treat (ITT) population is >0.

- **Analysis of secondary endpoints:**

The CGM endpoints will be analyzed using the same model as described for the primary endpoint using the ITT population.

Change in HbA1c will be analyzed using an ANCOVA model including the fixed categorical effects of treatment group (Toujeo, Tresiba), as well as, the continuous fixed covariate of baseline HbA1c value.

Change in FPG will be analyzed using ANCOVA model including the fixed categorical effects of treatment group (Toujeo, Tresiba), the randomization stratum of HbA1c at screening (<8.0%, ≥8.0%), as well as, the continuous fixed covariate of baseline FPG value.

Change from baseline in 7-point SMPG profiles (preprandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, and at bedtime) to Week 12 will be described by treatment group using mean and SD.

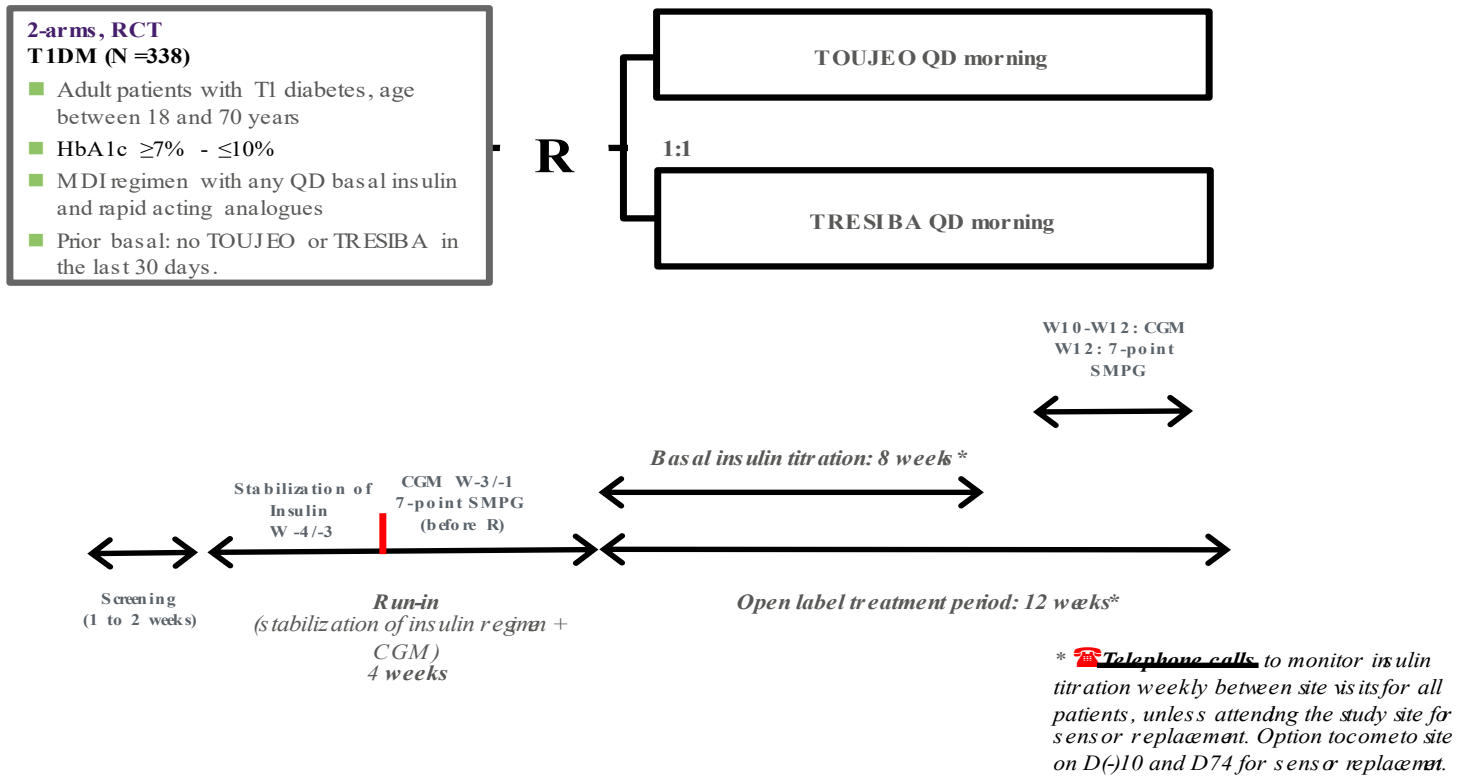
To control the type I error, a hierarchical step-down testing procedure described by Hochberg and Tamhane (3) will be applied for the primary efficacy endpoint and the main secondary endpoint:

- Step 1 proceeds to assess non-inferiority of Toujeo versus Tresiba on the percent time in range in 70-180 mg/dl,
- Step 2: only if step 1 is demonstrated, then non-inferiority of Toujeo versus Tresiba on the glucose total CV will be tested with a relative non-inferiority margin of 10%,
- Step 3: only if step 2 is demonstrated, then difference between Toujeo and Tresiba on the percent time in range in 70-180 mg/dl will be tested.

No multiplicity adjustment will be made on other secondary/other efficacy variables; 95% CI and P-values presented for these endpoints will be done for descriptive purpose only.

Data Monitoring Committee: No

1.2 SCHEMA



Abbreviations: CGM = continuous glucose monitoring, HbA1c = glycated hemoglobin, , MDI = multiple daily injection, R = randomized, SMPG = self-monitoring of plasma glucose, T1 diabetes = type 1 diabetes.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (weeks)	Run-in (weeks)				Intervention period (weeks)													Follow up	Notes
	-6/-5	-4	-3	-2	-1		1	2	3	4	5	6	7	8	9	10	11	12	EOT[c]	2 to 4 days after last IMP dose	Visit Windows: Site visits : ±3 days Phone call visits : ±1 day relative to Visit 6
Visit[a]	1	2	3	4 ☎	5 ☎	6	7 ☎	8 ☎	9 ☎	10 ☎	11 ☎	12 ☎	13 ☎	14	15	16 ☎	17 ☎	18[b]		19[d] ☎	
Day	-42/-35	-28	-20	-14	-7	1	7	14	21	28	35	42	48	56	64	71	78	84		86-88	
Informed consent	X																				To be repeated in case of rescreening
Inclusion/Exclusion criteria	X	X	X			X															
Demography	X																				
Full physical examination including height and weight	X																				
Medical history	X																				Medical, surgical and diabetes history
Method of mealtime insulin titration	X					X															Current method at screening and the one to be followed during treatment period at randomization
Vital signs and body weight	X					X								X				X	X		Vital signs include heart rate and blood pressure (sitting position)
Dispensation/collection of study diary		X	X			X								X	X			X	X		

Procedure	Screening (weeks)	Run-in (weeks)				Intervention period (weeks)													Follow up	Notes
	-6/-5	-4	-3	-2	-1		1	2	3	4	5	6	7	8	9	10	11	12	EOT[c]	2 to 4 days after last IMP dose	Visit Windows: Site visits : ±3 days Phone call visits : ±1 day relative to Visit 6
Visit[a]	1	2	3	4 ☎	5 ☎	6	7 ☎	8 ☎	9 ☎	10 ☎	11 ☎	12 ☎	13 ☎	14	15	16 ☎	17 ☎	18[b]		19[d] ☎	
Day	-42/-35	-28	-20	-14	-7	1	7	14	21	28	35	42	48	56	64	71	78	84		86-88	
Dispensation of study intervention						X								X							
IMP compliance check														X				X	X		Collecting and counting used and unused pens
IRT call[e]	X					X								X				X	X		
Randomization						X															
Documentation and review of basal and mealtime insulin dose	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior and concomitant medication	X	X	X			X					"			X				X	X	X	
CGM device dispensation ; blinded CGM and training including insertion of CGM sensor			X												X				X		If required, Investigators can arrange for patient's to attend the site after the first 10 days of CGM for the sensor to be replaced at the study site.
CGM recording[f]			20days												20 days			X			

Procedure	Screening (weeks)	Run-in (weeks)				Intervention period (weeks)													Follow up	Notes
	-6/-5	-4	-3	-2	-1		1	2	3	4	5	6	7	8	9	10	11	12	EOT[c]	2 to 4 days after last IMP dose	Visit Windows: Site visits : ±3 days Phone call visits : ±1 day relative to Visit 6
Visit[a]	1	2	3	4 ☎	5 ☎	6	7 ☎	8 ☎	9 ☎	10 ☎	11 ☎	12 ☎	13 ☎	14	15	16 ☎	17 ☎	18[b]		19[d] ☎	
Day	-42/-35	-28	-20	-14	-7	1	7	14	21	28	35	42	48	56	64	71	78	84		86-88	
Collect CGM device and upload CGM data						X												X	X		Upload CGM data to the site computer with QuintilesIMS Study Management Suite Software
Training: Glucometer, SMPG profiles, study diary		X																			
Glucometer dispensation		X																			
Fasting SMPG[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Values of last 3 measurements before each visit must be recorded in eCRF
2hPPG							X	X	X	X	X	X	X	X	X	X	X				Regularly as instructed by investigator
7-point SMPG						X												X	X		
SMPG data upload to site's PC						X								X	X			X	X	X	Server independent from eCRF
Re-training: Glucometer, SMPG profiles, study diary		X	X			X								X	X			X			

Procedure	Screening (weeks)	Run-in (weeks)				Intervention period (weeks)													Follow up	Notes
	-6/-5	-4	-3	-2	-1		1	2	3	4	5	6	7	8	9	10	11	12	EOT[c]	2 to 4 days after last IMP dose	Visit Windows: Site visits : ±3 days Phone call visits : ±1 day relative to Visit 6
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Day	-42/-35	-28	-20	-14	-7	1	7	14	21	28	35	42	48	56	64	71	78	84		86-88	
HbA1c, FPG	X					X												X[h]	X		Central lab h:In case of premature EOT, : HbA1c, FPG to be measured at Week 12
C-peptide	X																				Central lab
Hematology, clinical chemistry	X																				See Appendix 2, Section 10.2
Pregnancy test (WOCBP only)	X					X												X			Serum pregnancy test for screening; urine pregnancy test for subsequent monitoring (if positive to be confirmed by a serum test).
AE/SAE	To be assessed and reported if any throughout the study																				
Hypoglycemia recording	To be assessed and reported if any throughout the study																				
DTSQs						X												X			
DTSQc																		X			
MOS-sleep						X												X			

Procedure	Screening (weeks)	Run-in (weeks)				Intervention period (weeks)													Follow up	Notes
	-6/-5	-4	-3	-2	-1		1	2	3	4	5	6	7	8	9	10	11	12	EOT[c]	2 to 4 days after last IMP dose	Visit Windows: Site visits : ±3 days Phone call visits : ±1 day relative to Visit 6
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Day	-42/-35	-28	-20	-14	-7	1	7	14	21	28	35	42	48	56	64	71	78	84		86-88	
WPAI						X												X			

a Telephone calls to monitor insulin titration should be scheduled by the Investigator for Weekly in between of site visits for all patients, unless the patient is attending the study site for sensor replacement. Option to come to site on D-10 and D74 for sensor replacement.

b Visit 18 will occur at Week 12 regardless of the treatment end date, and procedures ticked below should be done

c EOT (End Of Treatment) visit will occur in case of premature discontinuation of study treatment before Visit 18 at week 12 and related procedures ticked below should be applied. If at the time of such premature discontinuation there is ongoing CGM recording, it should be completed, and EoT vist done thereafter. Afterward, the patients should continue in the study up to the scheduled date of study completion. See Section 7.1

d If EOT visit occurs beyond 2 to 4 days after last administration of study drug then Visit 8 will not be required. EOT and safety follow up can be done at the same time, if occurs within 2 to 4 days after last IMP dose.

e The Investigator should contact IRT either at Visit 18 or at EOT visit in case of premature end of treatment (whichever occurs first), to register end of treatment.

f For each 20 day CGM period to be fully evaluable for CGM it is necessary to obtain a minimum of 10 days (not necessarily consecutive) of useable CGM data. Useable CGM data for a day/a 24-hour CGM profile are defined as: at least 80% time of records per 24 hours; no gap (missing data) lasting for ≥2 hours per 24 hours besides the warm-up time for the sensor after insertion.

g SMPG to be performed by the patients from run-in period and throughout the study duration:

1. Fasting (pre-breakfast/pre-injection) SMPG: daily until dose stabilization of basal insulin 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 (pre-breakfast) SMPG measurements per week should be done.
2. SMPG values throughout the study, starting after Visit 2. Patients should test their SMPG following the Investigator's instructions for mealtime insulin titration.
3. 2hPPG (post prandial plasma glucose); regularly as instructed by investigator to guide meal time insulin titration;
4. 7-point SMPG profile (before and 2 hours after breakfast, lunch and dinner, and at bedtime): at least **ONE** day during the week that precedes Visits 6 and 18
   Patients should be instructed to self-assess plasma glucose levels whenever they experience any symptoms of hypoglycemia; see 'SMPG during symptomatic hypoglycemia' in Section 8.1.4 for further instructions.

Abbreviations: AE = adverse event, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, IMP = investigational medicinal product, IRT= interactive response technology, CGM = continuous glucose monitoring, EOT = end of treatment, PC = personal computer, R = randomization, SMPG = self-monitoring of plasma glucose, SAE = serious adverse event, WOCBP = women of childbearing potential.

2 INTRODUCTION

The fluctuations in blood glucose, regular short-duration periods of hyperglycemia and hypoglycemia, which are not detected by the measurements of HbA1c, may possibly contribute to vascular pathological processes and diabetic complications. This association may be independent of average glucose exposure expressed by HbA1c. This hypothesis remains controversial, but stems from the observation that intensive (versus standard) glucose control in the diabetes control and complications trial (DCCT) was associated with reduced risk for retinopathy after correcting for HbA1c (4). Supportive observations report that the coefficient of variation (CV) of fasting plasma glucose (FPG) independently predicted mortality in type 2 diabetes mellitus (T2DM) (5). Potential mechanisms that might link oscillating blood glucose with vascular pathology include oxidative stress and inflammatory processes, with enhanced apoptosis of vascular endothelial cells (6).

2.1 STUDY RATIONALE

In registration trials (EDITION and BEGIN), both Toujeo and Tresiba took Lantus as active comparator and demonstrated comparable efficacy and lower hypoglycemia risk. Toujeo and Tresiba are both described to have advantages over Lantus in their PK and PD profiles after once daily dosing regimens by providing a flatter fluctuation of PK exposure and a more evenly distributed GIR, which is considered desirable for a basal insulin.

The present study LPS14947 is designed to further explore similarities and differences between Toujeo and Tresiba in terms of the effect on continuous glucose profile, while the conventional glycemic control as measured by HbA1c is anticipated to be similar between the 2 treatments.

2.2 BACKGROUND

Insulin glargine U300 (HOE901-U300) is a more concentrated formulation of insulin glargine U100 (HOE901), 21A-Gly-31B-32B-Di-Arg human insulin, a recombinant analog of human insulin providing a 24 hour basal insulin supply after a single-dose SC injection. Insulin glargine U100 has been marketed as Lantus® for more than 15 years. 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 post marketing surveillance arising from approximately 30 million patient-years of clinical experience. The more sustained release of insulin glargine Toujeo (insulin glargine U300) compared to insulin glargine 100 U/mL is attributable to the reduction of the injection volume by two thirds that results in a smaller precipitate surface area. Further information on Toujeo, including important clinical trials performed pre and post registration, can be found in the National Product Label (7).

As observed in euglycemic clamp studies in patients with type 1 diabetes (PKD10086, PKD11627 and TDR11626) after a single dose or multiple doses in healthy subjects or patients with T1DM, there are differences between Lantus and Toujeo in PK/PD profiles. The prolonged and flatter profile of the glucose-lowering activity of Toujeo (up to 36 hours) results in more constant

glycemic control within a 24 hour injection interval and beyond, resulting in less circadian fluctuation in blood glucose levels and affording greater flexibility in dosing time (1). Given these features of the PK/PD profiles, Toujeo is considered to be well suitable for constant, peakless 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 Toujeo and Lantus with respect to glucose lowering, while a slightly lower risk of hypoglycemia was observed for Toujeo. Confirmed or severe nocturnal hypoglycemia was generally lower with Toujeo compared with Lantus, the incidence of confirmed or severe hypoglycemia at any time of day was equal or lower (8).

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 Toujeo or Lantus treatment. CGM analysis in participants with T1DM showed better glucose stability and lower intra-patient glucose variability with Toujeo than Lantus. These differences were more evident with the morning injection regimen. Moreover, the incidence of confirmed or severe hypoglycemic events was numerically lower with Toujeo than with Lantus. However, neither of the two studies was sufficiently powered to demonstrate reduced rates of hypoglycemia with Toujeo (9).

Tresiba is a basal insulin that forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation leading to a flat and stable glucose-lowering-effect. During a period of 24 hours with once-daily treatment, the glucose-lowering effect of Tresiba, was evenly distributed between the first and second 12 hours. This recombinant analog of human insulin provides basal insulin supply beyond 42 hours after injection in euglycemic clamp conditions in type 1 diabetes (2).

It has been approved in the US, European Union, Japan and other parts of the world. Further information on Tresiba can be found in the National Product Label (10).

The efficacy and safety of Tresiba were demonstrated in BEGIN program. The impact of Tresiba on HbA1c was comparable with insulin Lantus but with reduced risk of hypoglycemia mainly during the protocol defined nocturnal period (11).

A trial comparing the efficacy of insulin degludec with insulin glargine on glycemic control using CGM in patients with type 1 diabetes has shown that time within the glycemic target range (>70 mg/dL [>3.9 mmol/L] and <130 mg/dL [<7.2 mmol/L]) measured by CGM in the last 4 hours of each dosing interval during the last 2 weeks of the 6-week treatment period was 1.39 hours (SD 0.71) and 1.09 hours (0.77) respectively in insulin degludec and insulin glargine U100 arms respectively (12).

Study LPS14585 compared the PD and PK properties of 0.4 and 0.6 U/kg/day insulin glargine (Toujeo) with the same dose levels of insulin degludec (Tresiba). At a dose level of 0.4 U/kg/day at steady state, the individual fluctuations of the glucose infusion rate (GIR) over the dosing interval of 24 hours (GIR-smFL0-24) were significantly lower following treatment with Toujeo

compared to insulin degludec. The point estimate (90% CI) for the ratio of the PD parameter GIR-smFL0-24 for Toujeo versus insulin degludec was 0.80 (0.66 to 0.96) with a corresponding p-value of 0.047, indicating 20% less within-day variability of the glucodynamic profile for Toujeo versus insulin degludec in this clinically relevant dose (0.4 U/kg/day) for T1DM patients.

In a recent comparative RCT (BRIGHT trial) where Toujeo was directly compared to Tresiba in previously insulin-naïve patients with T2DM, non-inferiority was shown in efficacy while hypoglycemia was found to be lower for Toujeo in the insulin titration period (week 0-12) with comparable rates in the maintenance period (week 13-24) (13).

2.3 BENEFIT/RISK ASSESSMENT

Within the context of this Phase 4 study, a favorable risk-benefit assessment for the Investigational medicinal products (IMPs) (Toujeo and Tresiba) is already well established. The use of both drugs in this study is according to the approved National Product Label.

With the exception of minimal laboratory assessments at screening, the study procedures (including the use of CGM) are consistent with the standard-of-care for these patients. The risks arising from the minimal blood sampling required by the protocol and also for the CGM sensor placement (limited to infrequent occurrence of local skin reaction) are low.

Potential benefits to participants arise from the opportunity for treatment optimization and the availability of the CGM data following unblinding.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of Toujeo and Tresiba may be found in the Summary of Product Characteristics.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
To demonstrate the noninferiority of insulin glargine 300 U/mL in comparison to insulin degludec 100 U/mL on glycemic control and variability in participants with diabetes mellitus	Percent time in glucose range of ≥70 to ≤180 mg/dL (≥3.9 to ≤10 mmol/L) at Week 12, obtained using continuous glucose monitoring (CGM)
Secondary	
To evaluate the glycemic control and variability parameters in each treatment group at Week 12 using CGM	At Week 12, the following endpoints will be assessed: • Glucose total CV • Glucose within-day and between-day CV Other secondary endpoints: • Change from baseline to Week 12 in HbA1c • Change from baseline to Week 12 in central lab FPG • Percent time and mean hours per day with glucose<70mg/dL (on all time and during the night [00:00 to 05:59]) • Percent time and mean hours per day with glucose>180mg/dL
To evaluate the safety of insulin glargine 300 U/mL in comparison to insulin degludec 100 U/mL	Number of participants with adverse events (see Section 8.3) Number of participants with at least one hypoglycemic event from baseline to Week 12 Number of hypoglycemic events per participant year from baseline to Week 12
Tertiary/exploratory	
To explore the glycemic control and variability parameters in each treatment group at Week 12 using CGM	Mean hours per day in the glucose range of ≥70 to ≤180 mg/dL (≥3.9 to ≤10 mmol/L) Percent time and mean hours per day in the glucose range of ≥70 to ≤140 mg/dL (≥3.9 to ≤7.8 mmol/L) (on all-time and during the night [00:00 to 05:59]) Nocturnal percent time in glucose range of ≥70 to ≤180 mg/dL (≥3.9 to ≤10 mmol/L) at Week 12, obtained using CGM Percent time and mean hours per day with glucose: <54 mg/dL, (on all time and during the night [00:00 to 05:59]) Percent time with glucose <70 mg/dL within the 12 hours after basal insulin injection Percent time and mean hours per day with glucose >250 mg/dL Mean glucose profile over 24-hour period 24h-AUC

Objectives	Endpoints
	Daily insulin doses (total daily insulin, total basal insulin, total bolus insulin, ratio of basal to bolus insulin dose) in units and U/kg body weight
	Change from baseline to week 12 in patient-reported outcomes (treatment satisfaction, sleep quality and quantity, and productivity)
	7-point SMPG profiles (preprandial and 2-hour postprandial plasma glucose at breakfast, lunch dinner and bedtime) at Week 12 and change in 7-point SMPG profiles from baseline to Week 12

3.1 APPROPRIATENESS OF MEASUREMENTS

The primary efficacy endpoint is based on the CGM recording to be collected during Weeks 10-12, representing the last 3 weeks of the 12 week IMP (either Toujeo or Tresiba) treatment period by which time stable doses are anticipated (ie, IMP titration phase expected to be up to Week 8, see Section 6.6.1.2).

Secondary analyses will be performed to evaluate the therapeutic feature of a flatter and longer duration of Toujeo compared to Tresiba over at least 24 hours, which should result in more sustained glycemic control, and less hypoglycemia during nighttime. The assessment will be measured by the secondary and exploratory endpoints of: the incidence rate of nocturnal documented symptomatic hypoglycemia, and the variability analyses of CGM profiles.

The CGM system allows frequent glucose measurements (every 5 minutes) and the ability to analyze glucose distributions in real time (14, 15). 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.

Mealtime insulin titration will also be implemented to achieve the postprandial SMPG targets. Thus, the glycemic control measured by laboratory HbA1c and FPG at Week 12 is expected to be similar between the two treatments.

Frequent SMPG assessment values will be used to guide the insulin dose titration and to support the analyses of 7-point SMPG profile and hypoglycemia reports. At Visits 6, 14, 15 and 18 the SMPG data will be uploaded from the glucometer onto the site computer so that the Investigator and study staff are able to check the patient's comprehension and compliance with dose adjustments and diary completion and to identify potential non-reported episodes of hypoglycemia. Safety analyses include a thorough hypoglycemia analysis on incidence rate, proportion of patients with hypoglycemia and the diurnal distribution of hypoglycemia. These 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.

Sponsor will implement the monitoring of titration for both basal and meal time insulins to ensure optimal dosing.

Patient-Reported Outcomes (PRO):

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

The Diabetes Treatment Satisfaction Questionnaire Status and Change Versions (DTSQs and DTSQc, respectively) (16, 17) will be used to evaluate patient satisfaction with treatment and patient perception of blood glucose control over a several-week period.

The MOS Sleep questionnaire will be used to measure patient perception on key aspects of sleep (18). The WPAI will be used to measure absenteeism, presenteeism and work productivity (19).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multicenter, randomized, active-controlled, parallel-group, 12-week open-label study. The study consists of a 1- or 2–week screening period, followed by a 4-week run-in period, and a 12-week randomized treatment period.

During the first 2 weeks of the run-in period (Weeks -4 and -3), patients will undergo treatment stabilization of their current basal and mealtime insulin treatment, and will be trained and tested on how to perform study-related procedures. During the (-)3 – (-)1 weeks of run-in, patients will wear a CGM device, blinded both to patients and Investigators. This will be the baseline CGM period, when during 20 consecutive days, a minimum of (10 days, not necessarily consecutive) of useable CGM data must be generated, to be eligible for randomization.

Patients satisfying the study inclusion/exclusion criteria (including CGM performance requirements) will be randomized in a 1:1 ratio to morning injections of either Toujeo or Tresiba, which will replace the patient's current basal insulin.

An interactive response technology (IRT) will be configured and randomization will be stratified by HbA1c at screening (<8.0%; ≥8.0%).

During the randomized treatment period, CGM data (blinded to both patients and Investigators) will be collected during Weeks 9-12 during 20 consecutive days.

The basal insulin injection 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.

During the entire study starting after the screening period, patients will perform SMPG as specified in the study flow chart. The SMPG readings will be used to guide insulin dose titration for optimal glycemic control.

Appropriate dose titration of basal and mealtime insulin will be implemented as described in the dose regimen section.

At the end of the study, the patients will be followed-up from 2 to 4 days after last IMP dose to collect posttreatment safety information.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The fluctuations in blood glucose, regular short-duration periods of hyperglycemia and hypoglycemia, which are not detected by the measurements of HbA1c, may possibly contribute to vascular pathological processes and diabetic complications. This association may be independent of average glucose exposure expressed by HbA1c. This hypothesis remains controversial, but stems from the observation that intensive (versus standard) glucose control in the DCCT was associated with reduced risk for retinopathy after correcting for HbA1c (4). Supportive observations report that the coefficient of variation of FPG independently predicted mortality in T2DM (5). Potential mechanisms that might link oscillating blood glucose with vascular pathology include oxidative stress and inflammatory processes, with enhanced apoptosis of vascular endothelial cells (6).

This is a randomized, active-controlled, 12-week open-label study to compare the efficacy of Toujeo with Tresiba using CGM glucose profiles, sampling ambulatory glucose level every 5-minutes over a 20-day period at Week 12. The CGM during study period will be blinded to both the Investigators and patients.

Eligible patients will be randomized to either Toujeo or Tresiba, both given once-daily by SC injection in the morning. Patients allocated to Toujeo or Tresiba groups will switch from their previous basal insulin. During 4 weeks of the run-in period, patients will be required to titrate their basal and mealtime insulin to optimize the fasting and 2-hour postprandial self-monitoring of plasma glucose (SMPG) targets. The baseline CGM will be performed during the last 3 weeks of run-in.

The primary objective of the study is to explore the percent of time in target CGM glucose range of 70-180 mg/dL with Toujeo versus Tresiba treatment at 12 weeks of treatment. In addition, all hypoglycemia incidence and distribution (24 hours and nocturnal) will be analyzed according to the American Diabetes Association (ADA) classification (severe, documented symptomatic, asymptomatic, probable and relative) (20). Glucose stability and variability will be assessed between and within each group via measurements of glucose CV.

A relatively homogenous patient population will be selected, reducing potential confounding effects, so that the true differences in the therapeutic effects of Toujeo versus Tresiba 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 one year, and HbA1c level ≥7% and <10%. Patients must be on a stable dose of basal/bolus insulin regimen for 30 days before screening.

Repeat assessments of selected PROs will be performed during the study as the exploratory analyses (including patient satisfaction with treatment and patient perception of blood glucose control assessed by Diabetes Treatment Satisfaction Questionnaire [status and change version - DTSQs and DTSQc], MOS Sleep Scale to measure key aspects of sleep and the Work Productivity and Activity Impairment Questionnaire [WPAI]- Diabetes; assessing the impairment on daily work and activities due to diabetes) in order to reveal any potential link between improvement in continues glucose profile and patient well-being.

4.3 JUSTIFICATION FOR DOSE

During the first 2 weeks of the run-in period (Weeks -4 and -3), patients will be required to titrate their basal and mealtime insulin to stabilize the fasting and 2-hour postprandial SMPG targets of ≥70 to <100 mg/dL (≥3.9 to <5.6 mmol/L) while avoiding hypoglycemia episodes.

At randomization, the initiation doses of Toujeo and Tresiba will be the patient's current doses of their basal insulin on a unit-to-unit basis.

Dose adjustments will be based on a median of fasting SMPG values from the last 3 days, which will include the value measured on the day of titration, measured by the patient using glucometers and accessories supplied by the Sponsor. Appropriate dose titration of IMP and mealtime insulin is expected to be up to Week 8.

During the randomized treatment period, IMP injection will be administered once daily each morning at the same time.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including a 2 to 4 day follow-up period.

The end of the study is defined as the date of the "last patient last visit" planned with the protocol, including the follow-up visit.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 to 70 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with T1DM.

I 03. Participants treated with multiple daily injections (MDI) using basal insulin analog once daily and rapid acting insulin analogs for at least one year.

I 04. HbA1c ≥7% (48 mmol/mol) and ≤ 10% (86 mmol/mol) at screening.

Sex

I 05. Male or Female

a) Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4),

OR

b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the intervention period.

Informed Consent

I 06. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Any clinically significant abnormality identified either in medical history or during screening evaluation (eg, physical examination, laboratory tests, ECG, vital signs) , or any AE during screening period which, in the judgment of the investigator, would preclude safe completion of the study or constrains efficacy assessment.

E 02. End stage renal disease defined as estimated glomerular filtration rate (GFR) modification of diet in renal disease (MDRD) <15 mL/min/1.73 m² or on renal replacement treatment.

E 03. Laboratory findings at screening:

- ALT or AST >3 x ULN or total bilirubin >1.5 x ULN (except in case of documented Gilbert's syndrome).
- Fasting C-peptide >0.2 nmol/L.

E 04. Retinopathy or maculopathy with one of the following treatments, either recent (within 3 months prior to screening) or planned: intravitreal injections or laser or vitrectomy surgery.

E 05. Body weight change ≥5 kg within 3 months prior to screening

Prior/concomitant therapy

E 06. Participants not on stable dose of basal insulin analog (±20% total daily dose) for at least 30 days prior to screening.

E 07. Participants having received Toujeo or Tresiba as basal insulin within 30 days prior to screening.

E 08. Participants not using the same insulins (both basal and rapid) within 30 days prior to screening.

E 09. Participants having received basal insulin dose ≥0.6 U/kg body weight within 30 days prior to screening.

E 10. Participants having received any glucose lowering drugs (including any premixed insulins, human regular insulin as mealtime insulins, any others injectable or oral), other than basal and rapid insulin analogs, within 3 months prior to screening.

E 11. Participants having received glucocorticoids (excluding topical application or inhaled form) for more than 10 days within 3 months prior to screening.

E 12. Participants having used insulin pump within 6 months prior to screening.

E 13. Participants who will need real time, flash or implantable CGM for routine care any time during study participation.

Prior/concurrent clinical study experience

E 14. Exposure to any investigational drug in the last 4 weeks or 5 half-lives, whichever is longer, prior to screening or concomitant enrollment in any other clinical study involving an investigational study treatment.

Diagnostic assessments

Not applicable.

Other exclusions

E 15. Any contraindication to use of Toujeo, Tresiba and rapid insulin analogs according to the national product label.

E 16. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 17. Night shift workers.

E 18. Individuals accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized.

E 19. Participants dependent on the Sponsor or Investigator (in conjunction with section 1.61 of the ICH-GCP Ordinance E6).

E 20. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

Additional criteria at the end of the run-in period

E 21. Participants unwilling or unable to comply with study procedures as outlined in the protocol.

E 22. Participants who withdraw consent during the screening (starting from signed ICF).

E 23. Inappropriate CGM use during run-in period evidenced by failure to obtain a minimum of (10 days, not necessarily consecutive) of useable CGM data by the end of run-in (see Section 8.1.1.2 for the definition of useable CGM data).

5.3 LIFESTYLE CONSIDERATIONS

Lifestyle and diet therapy provided before the time of screening is to be continued during the study. Dietary and lifestyle counseling will be given by a healthcare professional and compliance will be checked as per SoA (Section 1.3) and should be consistent with international or local guidelines for patients with T1DM (with regard to the distribution of calories among carbohydrates, proteins, and fats, exercise, etc).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened in cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment. Rescreened patients will be subject to the screening visit procedures/assessments (see following paragraphs) including new informed consent signed and allocation of a new patient number.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

Study intervention name	Toujeo	Tresiba
Dosage formulation	Toujeo (insulin glargine 300 U/mL) is supplied as a sterile, non-pyrogenic, clear, colorless solution for SC injection in the Toujeo SoloStar prefilled, disposable pen.	Tresiba (insulin degludec 100 U/mL) is supplied as a sterile, non-pyrogenic, clear, colorless solution for SC injection in the marketed Tresiba FlexTouch prefilled, disposable pen.
Unit dose strength(s)/Dosage level(s)	Each Toujeo SoloStar contains in total 450 units of insulin glargine (1.5 mL of 300 U/mL insulin glargine solution). Mixing of Toujeo with other insulin products or dilution is not allowed	Each Tresiba FlexTouch contains in total 300 units of insulin degludec (3 mL of 100 U/mL insulin degludec solution). Mixing of Tresiba with other insulin products or dilution is not allowed.
Route of administration	SC self-injection	SC self-injection
Dosing instructions	Toujeo will be self-administered by SC injection once daily in the morning[a], which is defined as the time period between waking up and prebreakfast. 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. Injection site should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall or thighs or upper arms[b].	Tresiba will be self-administered by SC injection once daily in the morning[a], which is defined as the time period between waking up and prebreakfast. 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. Injection site should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall or thighs or upper arms[b].
Packaging and labeling	Toujeo SoloStar pens will be supplied as open label treatment kits containing 5 Toujeo SoloStar pens. Each SoloStar pen will be labeled as required per country requirement. Treatment labels will indicate the treatment number used for treatment allocation. The Investigator's name, the patient number and visit number will be entered manually by the site staff on the treatment box label prior to dispensing.	Tresiba FlexTouch pens will be supplied as open label treatment kits containing 5 Tresiba FlexTouch pens. Each FlexTouch pen will be labeled as required per country requirement. Treatment labels will indicate the treatment number used for treatment allocation. The Investigator's name, the patient number and visit number will be entered manually by the site staff on the treatment box label prior to dispensing.

a Patients taking their current basal insulin at any time (eg, evening) other than in the morning should switch their injection time to the morning at randomization. The instruction on changing injection time should be given by the Investigator in accordance with the National Product Label of the patient's current basal insulin. On the day of switching injection time, the total dose of current basal insulin and the pre breakfast (if applicable) rapid action insulin may need to be reduced based on the physician's medical judgment. For example, on the day before changing injection time, the dose of the current basal insulin may be changed to approximately 1/2 to 2/3 of the total daily dose, which would

then be injected in the evening as the patient's usual injection time. On the following day, the dose of randomly assigned basal insulin (IMP) will be equal to the total daily current basal insulin dose and injected in the morning before breakfast.

b Within a given area, location should be changed (rotated) at each time to prevent injection site skin reactions.The injection sites for IMP and noninvestigational medicinal product (NIMP) should be different so that, if any, an injection site reaction can be attributed specifically either to IMP (Toujeo or Tresiba) or NIMP (mealtime insulin).

INVESTIGATIONAL MEDICINAL PRODUCT(S)

An instruction leaflet, which explains how to use the disposable pen and needles, will be provided for Toujeo and Tresiba. All patients will be trained by study staff at Visit 6 (randomization) on how to use the pen correctly, how to rotate injection site to avoid skin reactions, how to store the pen and how to change the needle. Training will be repeated as often as deemed necessary by study site staff during the treatment period. For the duration of the treatment, patients will be required to use the same type of study drug disposable pens and needles. Each patient will be supplied with the appropriate number of pens according to the dispensing scheme indicated in the SoA (see Section 1.2).

Toujeo (insulin glargine 300 U/mL)

Toujeo will be self-administered with the prefilled, disposable Toujeo SoloStar pen specifically labeled for use in the study. This pen allows dose setting in the range of 1–80 units with minimum of 1 unit increment. The dose of Toujeo is titrated according to the patient's need for insulin glargine.

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

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

Tresiba (insulin degludec 100 U/mL)

Tresiba will be self-administered with the prefilled, disposable Tresiba FlexTouch pen specifically labeled for use in this study. This pen allows dose setting in the range of 1–80 units with minimum of 1 unit increment. The dose of Tresiba is titrated according to the patient's need for insulin degludec

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

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

NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

The protocol-mandated background therapy is mealtime insulin analog, ie, rapid insulin analogs (eg, insulin glulisine, insulin lispro or insulin aspart). Patients in both treatment groups will continue with their short-acting mealtime insulin analogue which has been used for at least 30 days before the screening visit and which will be continued throughout the study. The cost of the mealtime insulin analogue may be reimbursed if not covered by health insurance and if allowed by local regulations. Alternatively, the sponsor provided insulin glulisine may be offered.

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

6.1.1 Devices

CGM

Dexcom G6 device will be used for continuous glucose monitoring.

Glucometers

Roche Accucheck glucometers will be provided and used for SMPG measurements by patients.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP/NIMP/device (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.6).

A potential defect in the quality of IMP/NIMP/device 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 the IMP/NIMP/device and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/NIMP/device to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMP/NIMP/device to be used other than as directed by this clinical trial protocol, or dispose of IMP/NIMP/device in any other manner.

The expiry date is mentioned on the IMPs labels, and storage conditions are written on the IMPs labels and in the instruction leaflet. Patients are responsible for the correct storage of “not in-use” and “in-use” pens after it is dispensed at the site.

All used, partially-used or unused treatments 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 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.

As NIMP will not be provided by the Sponsor, return and destruction will not be required. The cost of the mealtime insulin analogue may be reimbursed if not covered by health insurance and if allowed by local regulations. Alternatively, the sponsor provided insulin glulisine may be offered.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

As Toujeo and the control drug Tresiba are distinguishable, this study is an open-label design, and no attempt will be made to blind the randomly assigned study treatment.

The Clinical Supplies Trial Supply Operations Manager will provide the treatment kit number list and the Study Biostatistician will provide the randomization scheme to the IRT. IRT will then generate the patient randomization list according to which it will allocate patients to either treatment arm.

The IMPs will be provided in open-label boxes and each type of kit is identified with a treatment number.

At the screening visit, the Investigator or designee will contact the IRT center to receive the patient number. This patient number is composed of a 12-digit number containing the 3-digit country code, 4-digit center code, and the 5-digit patient chronological number (which is 00001 for the first patient screened in a center, 00002 for the second patient screened in the same center, etc).

Patients can be re-screened once before randomization in case of non-eligibility or in cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment. Re-screened patients will be subject to the screening visit procedures/assessments including new informed consent signed and allocation of a new patient number.

Before randomization, baseline CGM results with accompanying CGM summary report certifying compliance with requirements MUST be available. In order for a patient to be randomized the baseline CGM performance (during Weeks -3 to -1) must reflect at least 10 days (not necessarily consecutive) of useable 24-hour CGM data (see Section 8.1.1.2 for the definition of useable data).

At Visit 6, only after patient eligibility is confirmed, the Investigator or designee will call the IRT for patient randomization and first treatment kit(s) allocation.

Only eligible patients will be randomized at a 1:1 ratio to receive Toujeo or Tresiba for 12 weeks. Randomization will be stratified by HbA1c at screening (<8.0%; ≥8.0%).

A randomized patient is defined as a patient who is registered and assigned with a randomized treatment arm from the IRT, as documented from IRT log file, regardless of whether the treatment kit was used or not.

The IRT will be contacted at each time a treatment kit(s) allocation is necessary, ie, at Visit 6 (randomization) and also at Visit 14.

A patient cannot be randomized more than once to the study.

Complete details of potential instances requiring the site to contact the IRT are provided in Section 1.3.

Compensation for lack of blinding

Given the open-label administration of study treatments (basal insulin during the treatment period), the assessment of outcomes will be based on objectively collected data, which will be blinded for CGM (primary and secondary endpoints) and open for SMPG data (secondary endpoints).

Neither the patient, the Investigator nor the Sponsor will have access to the individual data for the primary efficacy parameter (CGM records) obtained from each patient so as to avoid patients and Investigators making treatment decisions based on the data for the primary endpoint. The CGM receiver's screen will be blocked of displaying data. The CGM data will be uploaded to a separate server which assures maintenance of the blind with vendor software 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. However, transfers of CGM related to the Sponsor team will be performed during the study for data review purpose, with the name of the IMP treatment masked.

The SMPG records in the patient diaries (and complete data at study visits where there is a download of SMPG data) enable Investigators to monitor the patients comprehension of the study requirements, identify unreported episodes of hypoglycemia, and also to guide the dose of basal (current during run-in, IMP during the randomized treatment period) and mealtime insulin dosage; hence these data are not blinded for the Investigator and the patient as they are required for managing the patient's care during the study.

The Sponsor study team, except individuals who have access to patients' source documents (eg, local monitoring team, auditors) will remain blinded to the treatment arm of individual patients throughout the study up to the database lock. All analyses and data review before database lock will be performed blindly. Supplemental documentation will detail the exact measures to be kept in place to manage the risk of inadvertent unblinding of the study team.

6.4 STUDY INTERVENTION COMPLIANCE

6.4.1 Drug accountability

A Treatment Log Form for returned and dispensed IMP will be kept for each patient. Patients will return to the site with used and unused IMP at Visits 14 and 18. The Investigator or delegate will inspect IMP remaining in the returned packs and compare to dosing records documented in the patients' diaries. Discrepancies will be addressed to the patient for clarification on treatment compliance. The Investigator will complete the appropriate Treatment Log Form based on the used/unused IMP (study drug pens) returned.

6.4.2 Training to use injection devices

An instruction leaflet, which explains how to use the disposable pen and needles, will be provided for Toujeo and Tresiba. All patients will be trained by study staff at Visit 6 (randomization) on how to use the pen correctly, how to rotate injection site to avoid skin reactions, how to store the pen and how to change the needle. Training will be repeated as often as deemed necessary by study site staff during the treatment period. For the duration of the treatment, patients will be required to use the same type of study drug disposable pens and needles. Each patient will be supplied with the appropriate number of pens according to the dispensing scheme indicated in the SoA (see Section 1.3).

Patients must be reminded by study staff of the following instructions: 'Injection pens should never be shared with others, even if the needle is changed. Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person'.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

During the study, the following medications are prohibited.

- Any glucose-lowering agents other than:
  - the IMP (Toujeo or Tresiba),
  - the patient's current background basal insulin analog during the run-in period (which may not be changed during the study),
  - the patient's existing mealtime insulin (which may not be changed during the study).

  This includes oral or injectable glucose lowering agents, other type of basal insulin (eg, NPH), 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).

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.

6.6 DOSE MODIFICATION

Note: During the first 2 weeks of the run-in period, patients will be required to titrate their basal and mealtime insulin to stabilize the fasting and 2-hour postprandial self-monitoring of plasma glucose (SMPG) targets.

6.6.1 Basal insulin

The patient's basal insulin dose will be titrated with the objective of reaching a target fasting SMPG of ≥70 to <100 mg/dL (≥3.9 to <5.6 mmol/L) while avoiding hypoglycemia episodes (ie, this is identical to the algorithm to be used for IMP see Section 6.6.1.2). Note: fasting SMPG should be taken within 30 minutes prior to injection of current basal insulin (if applicable) and before breakfast.

6.6.1.1 Starting dose

At randomization, the initiation doses of Toujeo and Tresiba will be the patient's current doses of their basal insulin on a unit-to-unit basis.

The first injection of IMP should occur on the day of randomization (Visit 6) under the supervision of the 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 electronic case report form (eCRF) for randomized basal insulin (IMP).

6.6.1.2 Dose adjustment

6.6.1.2.1 Dose adjustments based on target fasting SMPG

During the titration phase (expected to be up to Week 8), doses of IMP (either Toujeo or Tresiba) will be titrated to achieve glycemic targets without hypoglycemia according to the algorithm outlined in Table 3.

The IMP dose will be titrated at least weekly (but no more often than every 3 days), until the patient reaches a target fasting SMPG of ≥70 to <100 mg/dL (≥3.9 to <5.6 mmol/L) while avoiding hypoglycemia episodes.

Dose adjustments will be based on a median of fasting SMPG values from the last 3 days, which will include the value measured on the day of titration, measured by the patient using glucometers and accessories supplied by the Sponsor.

Table 3 - Basal insulin dose adjustments

Median[a] fasting pre-breakfast SMPG values (last 3 days)	Basal insulin dose adjustments (U/day)[b]
≥140 mg/dL (≥ 7.8 mmol/L)	+4 units
≥100 and < 140 mg/dL (≥5.6 and <7.8 mmol/L)	+2 units
≥70 and <100 mg/dL (≥3.9 and <5.6 mmol/L)	No change
≥56 and <70 mg/dL (≥3.1 and <3.9 mmol/L)	-2 units
<56 mg/dL (<3.1 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or 1 severe hypoglycemic episode	-4 units or at the discretion of the Investigator or medically qualified designee

Abbreviation: SMPG = self-monitoring of plasma glucose

a Median refers to intermediate SMPG value (the value between the lowest and the highest SMPG values when the values are ranked in a growing order).

b Prior to additional basal insulin titration, mealtime insulin should be titrated to achieve a bedtime and pre-breakfast glucose delta <50 mg/dL, if so considered helpful by the Investigator.

Regular SMPG is very important in order to achieve blood glucose targets. It is necessary to perform daily fasting/pre-breakfast SMPG and postprandial measurements (Section 8.1.4) to support the titration. More frequent SMPG at other time-point 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, contacts between the Investigator and patient are scheduled to assess the response to treatment and to decide on dose adjustment. During these visits, 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.

The best efforts should be made to reach the target glucose by 8 weeks after randomization; thereafter, the dose should be maintained until the end of the study. If required, minimal dose adjustments may be considered at the discretion of the Investigator or medically qualified designee to achieve fasting SMPG target.

6.6.1.2.2 Dose adjustment in cases of hypoglycemia

Dose adjustment in cases of hypoglycemia will be as follows (refer to Section 8.2.4 for hypoglycemia definitions):

- Upward titration is to be stopped for 1 week after a case of severe hypoglycemia (requiring assistance) or ≥2 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 (IMP during the randomized treatment period and patient's current medication during the run-in period) or mealtime insulin may be reduced or modified at any time for hypoglycemia during the study.
- Small decreases of the basal insulin dose (eg, 1 unit) are at the discretion of the Investigator or medically qualified designee, if SMPG is below 70 mg/dL (3.9 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.

6.6.2 Mealtime insulin

From Visit 2, the injection time (in relation to the meal intake) and frequency of mealtime insulin (ie, rapid-acting insulins: insulin glulisine, insulin lispro or insulin aspart) will be at the Investigator's discretion, in accordance with the relevant National Product Labels.

The dose of the mealtime insulin analogs will be actively 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 from the prior 3 days (simple titration based on a pattern of post-meal glucose median <130/>180 mg/dL) 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 to ≤180 mg/dL (≥7.2 to ≤10 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.

Dose of mealtime insulin will be recorded in the patient's diary and eCRF. **Note:** It is essential that this data is captured on the day of randomization.

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 study (Visits 2 to 18).

The two regimens are described in Table 4 and Table 5.

Table 4 - Rapid-acting insulin dose adjustment

Mealtime dose of insulin	Pattern of postprandial plasma glucose values <130 mg/dL[a]	Postprandial plasma glucose 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 half of the mealtime plasma glucose (2-hour postprandial plasma) values for the week were above target.

Table 5 - Carb counting: insulin-to-carbohydrate ratio

Mealtime dose of insulin	Pattern of postprandial plasma glucose values <130 mg/dL[a]	Pattern of postprandial plasma glucose 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 half of the mealtime plasma glucose values for the prior 3 days were above target
Starting recommendation 1 unit 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.

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

6.6.3 Monitoring of insulin titration

Sponsor will ensure the adequate monitoring of basal and mealtime insulin titration. The monitoring will be described in the Insulin-Dosing Supervision Manual.

6.6.4 Evaluation of participants not meeting glycemic targets

In case the target fasting glycemic goal cannot be achieved in spite of successive IMP dose titration over 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 AE)/ SAE/concomitant medication parts of the eCRF,
  - 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.

6.7 INTERVENTION AFTER THE END OF THE STUDY

Intervention after the end of the study treatment is at the discretion of the Investigator or other treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive 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; definitive IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF. In any case, the participant should remain in the study as long as possible.

Definitive intervention discontinuation is any intervention discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP whatever the reason.

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 reason(s) for treatment discontinuation and this should be documented in the eCRF.

The patients may withdraw from treatment with IMP in case of the following:

- At patient's own request, ie, withdrawal of the consent for treatment.
- If, in the Investigator's opinion, continuation with the administration of IMP would be detrimental to the patient's well-being.
- At the specific request of the Sponsor.

A patient must withdraw from treatment with IMP in either of the following cases:

- Intercurrent condition that requires discontinuation of IMP.
- Pregnancy in female participants.
- Necessity to use prohibited therapy (see Section 6.5)

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

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures 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.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP (Visit 18). If CGM assessment is ongoing it should be completed as planned for the ongoing 2-week period.

After that patients should remain in the study and complete all relevant scheduled study assessments. Whenever possible, CGM should be performed on Weeks 10 - 12, and patient return for the planned Visit 18.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs or for other reason.

For all temporary treatment discontinuations, duration must be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.2.1 Rechallenge

In case of treatment interruption due to an AE, 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(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

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

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

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

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 EFFICACY ASSESSMENTS

8.1.1 Continuous glucose monitoring (CGM)

A CGM system is a device that records interstitial glucose levels continuously throughout the day and night via a subcutaneous sensor. During the study, patients will use the Dexcom G6® CGM system with software (DexCom, Inc., San Diego, CA), an approved device with single-use disposable electrochemical sensing elements designed for up to 10 days of continuous use with measurement of glucose levels in interstitial fluid in 5-minute intervals.

All patients must use the CGM device provided by the Sponsor during the CGM collection periods. Additionally, patients cannot initiate personal (non-study) real time, flash or implantable CGM system during the study (see E 13).

8.1.1.1 CGM performance

Two (2) sets of CGM will be conducted by the study patients. Baseline CGM will start at Visit 3 (Week -3) and stop at randomization visit (Visit 6). During the randomized treatment period, an endpoint CGM recording during Weeks 9, 10, 11 and 12 [Days 64 to 84]) will be done. Patients must be well trained to understand the importance of the CGM performance and compliance with the manufacture's (DexCom) instructions.

All patients will undergo training, delivered by the investigational site personnel, at Visit 2 regardless of previous experience with CGM. After the training, patients should understand the process of CGM and how to handle the CGM device at home, the distance of receiver and effect of temperature on the device etc. If the patient is not sufficiently compliant with the study procedures, all necessary training has to be repeated by the site staff.

Patients, Investigators, and study personnel will be blinded to the CGM data. The CGM receiver's screen will be blocked of displaying data. Neither patients nor Investigators will be able to see the glucose values.

At Visit 3 and Visit 15, the insertion of CGM sensor will occur under the supervision of Investigators or designees. Patients will be instructed to insert the sensor into the belly (abdomen) at least 8 cm (3 inches) away from the insulin injection sites.

After the CGM sensor being inserted, and the transmitter being attached, patients will stay in the study site as long as needed to explain the use of CGM. During the next 19 days when the patients are operating the CGM, they must:

- 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.
- After 10 days of wearing the device, patients must remove and replace the sensor themselves. **Note:** If required, Investigators can arrange for patients to attend the site after the first 10 days of CGM for the sensor to be replaced at the study site.

Patients will receive a user guide of instruction included in the DexCom G6 device kit. Technique support via a 24/7 help-line service for trouble shooting will be provided by the manufacturer, DexCom. The patients should immediately contact the sites if they encounter any device 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.

After the end of the study, the patients and their Investigator will receive a standardized analysis (eg, Ambulatory Glucose Profile) of their personal two 20-day CGM-periods.

8.1.1.2 CGM qualification and data transfer

CGM qualification

There are 2 periods of CGM in this study. During each CGM period, patients will wear the CGM for 20 consecutive days to generate a minimum of (10 days, not necessarily consecutive) of useable CGM records. Useable CGM data for a day/a 24-hour CGM profile are defined as:

- At least 80% time of records per 24 hours.
- No gap (missing data) lasting for ≥2 hours per 24 hours besides the warm-up time for the sensor after insertion.

Note: Only patients with 10 days out of 20 of qualified CGM records will proceed to randomization and other CGM recording periods.

CGM data transfer

The CGM data will be uploaded to a separate server which assures maintenance of the blind with vendor software (QuintilesIMS Study Management Suite) and a data acceptability report with daily CGM performance will be available immediately. This will be performed at the end of the 20-day CGM period and may additionally be generated in the event of a patient returning to the site for replacement of the sensor after the first 10 days of CGM. 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 and will be considered as source documents).

Use of CGM data for future analysis

After the database lock anonymized CGM data may be transferred to a third party for future analysis and modeling of glycemic values.

8.1.2 Glycated hemoglobin A1c

Glycated hemoglobin A1c is assayed at screening (Visit 1; Week -6/-5), randomization Visit 6 and Visit 18 (Week 12). For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I "National Glycohemoglobin Standardization Program", or equivalent certification as per specific country regulations, central laboratory. The screening value will be transferred into the IRT for stratification purpose during the patient randomization at the Visit 6.

8.1.3 Fasting plasma glucose

Fasting plasma glucose is measured at a central laboratory. Blood samples for FPG measurement are taken at screening (Week -6/-5), randomization Visit 6 and at Visit 18 (Week 12).

8.1.4 Self-monitoring of plasma glucose

Plasma glucose values will be self-measured by the patients using the Sponsor-provided glucometers and corresponding supplies (lancet, control solutions, test strips, etc). Patients should not use their own glucometers during the study period starting after Visit 2 (Week -4).

Self-monitoring plasma glucose performance

At Visit 2, the patients will be shown how to accurately measure plasma glucose values with the blood glucometers. 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 will be repeated as often as necessary at the study visits and the investigational staff will review the study diary at each visit.

The schedule for performing SMPG is specified in Section 1.3.

Self-monitoring of plasma glucose 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 visit and also ask the pattern of fasting and postprandial SMPG 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. The SMPG records will be the patient's study diary entries (available at each visit). The SMPG summary report downloaded at Visits 6, 14, 15 and 18 will also be available to Investigators.

Investigators will record SMPG values and insulin doses during weekly telephone contacts as well.

Fasting self-monitoring of plasma glucose

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

Pre-injection SMPG: Within 30 minutes prior to injection of Toujeo or Tresiba before breakfast on the day of the first injection of the IMP (Day 1/Visit 6) and daily until uptitration has been completed and fasting pre-breakfast SMPG is stable in the target range, and then, at least 3 fasting measurements per week.

2 hours PPG will be measured by patient regularly as instructed by investigator to guide the dosing of meal time insulin.

7-point SMPG profiles

Before (pre-injection after randomization) and 2 hours after breakfast; lunch; dinner, and at bedtime: at least 1 day during the week that precedes Visits 6 and 18. Note: 7-point SMPG profile should also be pre-injection during the run-in period in cases where the patient's current basal insulin is administered in the morning.

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 self-assess 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 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 eCRF. This includes all symptomatic hypoglycemia events and asymptomatic hypoglycemia. Investigators should review the SMPG diary entries (and when available also data stored in the glucometer) to assess data for episodes of hypoglycemia, ie, to confirm episodes reported by patients in the diary and also to identify any episodes that were not reported in the diary).

Hypoglycemia events fulfilling the criteria of a SAE will also be documented on the AE and SAE form in the eCRF.

Recording of SMPG data

Patients will document their SMPG values with the testing times in the Sponsor-provided diary. If for any reason, 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 diary can be kept in the study source documents.

At on-site Visits 6, 14, and 18, SMPG data stored in the individual's glucometer will be uploaded to the site's computer. A summary including all measured glucose values will be promptly available for the Investigator (or designee) to review. SMPG data will be uploaded to site's PC (server independent from eCRF). At a minimum, for SMPG data that are captured in the eCRF, including the values recorded during weekly telephone contacts, the Investigators or study staff must verify the accuracy with the data that are uploaded from the glucometer. 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.

Use of SMPG data for future analysis

The SMPG data from the glucometer will be uploaded to an independent server and will not be captured in the clinical database (which will comprise SMPG data that is transcribed from the study diary).

The downloaded SMPG data will not be analyzed or reported in the clinical study report.

After the database lock anonymized SMPG data may be transferred to third party for future analysis and modeling of glycemic values.

8.1.5 Insulin dose (including IMP during the treatment period)

Insulin dose and injection time for both basal insulin (ie, patient's current basal insulin prior to randomization or IMP [Toujeo or Tresiba] after randomization) and mealtime insulin will be documented in the study 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.

- At Weeks 4, 8, and 12, the following data will be entered in the eCRF:
  - The dose the patient was taking prior to the visit and the dose taken after the visit (so as to reveal any dose adjustments made at the visit),
  - All available data on the injection time and doses administered will be entered in the eCRF, 1 week before on site visit, including missed injection,
  - Missed injections.
- In case of symptomatic hypoglycemia, the dose and injection time should be entered in the eCRF on the specific hypoglycemia form.

- All available data of dose and injection time on the last 3 days before permanently IMP treatment discontinuation.
- Data on SMPG values and dose of basal and rapid acting insulin, obtained verbally during weekly telephone contacts.

8.1.6 Patient-reported Outcomes (PROs)

The patient-reported outcome (PRO) questionnaires in this study are the Treatment Satisfaction Questionnaire (DTSQs and DTSQc versions), the MOS Sleep and the Work Productivity and Activity Impairment Questionnaire (WPAI).

The patients will be requested to complete all the questionnaires by themselves during selected clinical visits (see study SoA), independently from investigator, site staff and any help from friends or relatives. For validity purposes, patients will be asked to answer all the questions of the questionnaires at the start of the visit in a quiet place, and while on site to return the completed questionnaires on the same day.

In case of premature discontinuation of study treatment, all the PRO questionnaires will be completed by the patients as normally planned at 12 weeks.

8.1.6.1 DTSQs

The Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs) will be used to evaluate patient satisfaction with treatment and patient perception of blood glucose control over a several week period (16). The DTSQs is a validated questionnaire comprised of 8 questions which are answered on a Likert scale from 0 to 6. Responses to 6 of the items will be summed to produce a Total Treatment Satisfaction score ranging from 0 (no satisfaction) to 36 (high satisfaction with treatment). The 2 items of 'perceived frequency of 'hyperglycemia' (Item 2) and 'perceived frequency of hypoglycemia' (Item 3) are scored separately ranging from 0 (none of the time) to 6 (most of the time). The DTSQs will be completed by the patients at baseline and Week 12. Mean differences in scores from baseline and between groups will be evaluated to understand the impact of treatment on patient satisfaction.
The DTSQs is available in appendix 5 (Section 10.5).

8.1.6.2 DTSQc

The Diabetes Treatment Satisfaction Questionnaire Change Version (DTSQc) was developed from the original DTSQ to evaluate the change in treatment satisfaction at a specific time point. The DTSQc instructions and response options differ from those of the DTSQs to produce measures of relative change in satisfaction rather than measures of absolute satisfaction.

It will be used to measure patient perception of change in treatment satisfaction at 12 weeks. Scores for DTSQc treatment satisfaction items range from −3 to +3, and the sum of the treatment satisfaction score range from −18 to +18. Positive scores are indicative of improvement in treatment satisfaction, whereas negative scores are indicative of deterioration in treatment satisfaction since start of the study. Perceived frequency of hyperglycemia and hypoglycemia

scores range from −3 to +3, with negative scores indicating fewer problems with blood glucose levels and positive scores indicating more problems than before. DTSQc will be completed by the patients at 12 weeks after the DTSQs (status version). To control for baseline scores, DTSQs will be used as a measure of treatment satisfaction at baseline.

The DTSQc is available in appendix 5 (Section 10.5).

8.1.6.3 MOS Sleep

Originally developed for use in the Medical Outcomes Study (MOS), the MOS Sleep Scale is a brief, self-administered generic assessment designed to measure key aspects of sleep, such as disturbance, adequacy, somnolence, and quantity.

The 12-item acute revised version of the MOS Sleep will be used in this study with a past week recall period and 5-point likert response options (appendix 5 in Section 10.5.3).

The 12-item MOS Sleep Scale assessment yields scores on six subscales (18, 21):

- Sleep Disturbance (4-item subscale on sleep initiation problems, and sleep maintenance problems).
- Snoring (single-item subscale).
- Shortness of Breath or Headache (single-item subscale asking about the frequency of awakening with shortness of breath or with a headache).
- Sleep Adequacy (2-item subscale asking about frequency of awakening fresh and rested in the morning and getting the amount of sleep needed).
- Daily Somnolence (3-item subscale).
- Sleep Quantity (single-item subscale representing the average number of hours slept).
- One Sleep Problems Index is also calculated based on 9 of the items.

Responses to all but the open-ended sleep quantity item are transformed to scores on a 0-100 metric, with higher item scores reflecting more of the attribute implied by the scale name. Scores on the multi-item subscales and indexes also range from 0 to 100.

The MOS Sleep will be completed by the patients at baseline and Week12.

8.1.6.4 WPAI

The WPAI is a 6-item validated questionnaire assessing the amount of absenteeism, presenteeism and daily activity impairment attributable to a specific health problem (WPAI:SHP version V2.0) (19). An adapted version of the WPAI:SHP will be used where the term PROBLEM was replaced by DIABETES, as requested by the authors.

The WPAI:Diabetes will be completed by the patients at baseline and Week 12.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

A complete physical examination will include, at a minimum, assessments of the [Cardiovascular, Respiratory, Gastrointestinal and Neurological] systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Vital signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure and pulse.

Blood pressure (mmHg) should be measured when the patient is quiet and seated and with their arm outstretched in line with mid-sternum and supported. Measurement should be taken under standardized conditions, approximately at the same time of the day, on the same arm, with the same device and the values are to be recorded in the eCRF. Devices for blood pressure measurement should be regularly recalibrated according to manufacturers' instructions.

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

8.2.3 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.4 Hypoglycemia

Hypoglycemia will be reported on the specific hypoglycemia event information form of the e-CRF. Hypoglycemia fulfilling the seriousness criteria will be documented in addition on the SAE form in the e-CRF.

The SMPG values will be used for the confirmation of hypoglycemia (ie, episodes both reported and not-reported by patients in the diary).

Hypoglycemic events will be categorized (20, 22, 23, 24) 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 participants at risk for injury to themselves or others. Note that "requiring assistance of another person" means that the participant could not help himself or herself. Assisting a participant out of kindness, when assistance is not required, should not be considered a "requiring assistance" incident. Severe hypoglycemia will qualify as an SAE only if it fulfills SAE criteria (see Section 10.3). For example, events of seizure, unconsciousness or coma must be reported as SAEs.
- **Documented symptomatic hypoglycemia:** Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than 3.9 mmol/L (70 mg/dL). 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 3.9 mmol/L (70 mg/dL).

In addition to the threshold of plasma glucose of less than 3.9 mmol/L (70 mg/dL), documented hypoglycemia with a measured plasma glucose concentration less than 3.0 mmol/L (54 mg/dL) will also be analyzed (20, 24).

Hypoglycemic events will be evaluated regardless the time of onset during the study and time of the day.

In addition, hypoglycemia events will be evaluated at the following time periods defined by time of the day:

- Nocturnal hypoglycemia: any hypoglycemia of the above categories that occurs between 00:00 and 05:59, regardless of whether participant was awake or woke up because of the event.
- Daytime hypoglycemia: any hypoglycemia of the above categories that occurs between 06:00 and 23:59.

Note: CGM values will not be taken into account for the purpose of hypoglycemia.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) 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, modified or removed during a study by protocol amendment.

The AESIs are listed below:

- 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 participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]),
  - 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 (See Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or non-serious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic drug count) and defined as any dose administration which, in the Investigator's opinion based on clinical judgment is considered significantly greater than the prescribed dose of insulin.

    Of note, asymptomatic overdose has to be reported as a standard AE.

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AE will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, [and non-serious AEs of special interest (as defined in Section 8.3)], will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected will be specified in the product prescribing information.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants occurring after the start of study intervention and until the end of the study will be collected and followed until the outcome.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Guidelines for reporting product complaints

Any defect in the IMP/NIMP/device must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.

3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

PK parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

Biomarkers are not evaluated in this study.

8.9 HEALTH ECONOMICS

Health economics are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The objective is to show non-inferiority of Toujeo versus Tresiba in patients with type 1 diabetes on the percent time in glucose range of ≥70 to ≤180 mg/dL (≥3.9 to ≤10 mmol/L) at Week 12 obtained using CGM.

9.2 SAMPLE SIZE DETERMINATION

The sample size calculation is based on the percent time spent in glucose range of ≥70 to ≤180 mg/dL (≥3.9 to ≤10 mmol/L) at Week 12, assessed from CGM measurements obtained during Weeks 10, 11 and 12.

For this criterion of percent time in range, there is no predefined non-inferiority margin. A relative non-inferiority margin of 10% is considered.

Let m1 and m0 be the true means for the Toujeo and Tresiba groups, respectively.

The non-inferiority null hypothesis would be H0: m1-m0 ≤ -0.1*m0 or H0: m1-0.9*m0 ≤0 and the alternative hypothesis (H1): m1=m0.

Toujeo would be considered non-inferior to Tresiba if the lower limit of the 95% CI for the adjusted difference estimate of m1-0.9*m0 at Week 12 is >0.

To ensure 90% power, the sample size should satisfy:

$$1.96 - \frac{(0.1 * m0)}{\sqrt{\frac{1.81 * SD^2}{n}}} = -1.282$$

Where -1.282 is the 10th percentile of a standard normal distribution and SD the common SD.

Which leads to:

$$n = \frac{(1.96 + 1.282)^2 * 1.81 * SD^2}{(0.1 * m0)^2}$$

Assuming a common SD of 14.7%, an average percent time in range in the Tresiba treatment group of 56% (value from LPS14587), no true difference between both arms under H1, and a relative non-inferiority of 10%, a sample size of 131 evaluable patients per treatment group would provide at least 90% power to show non-inferiority of Toujeo with respect to Tresiba on the percentage of time plasma glucose within the range of ≥70 to ≤180 mg/dL at Week 12.

With the assumption of a non-evaluability rate of 22% 338 participants (169 per treatment arm) will have to be randomized.

Patient is evaluable for the primary endpoint if he/she as at least 10 days of useable CGM data (not necessarily consecutives) at Week 12 (see Section 8.1.1.2 for definition of useable data).

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 6):

Table 6 - Populations for analyses

Population	Description
ITT	All randomized (patients who signed ICF and with a treatment arm allocated before first IMP and recorded in the IRT database) participants, irrespective of the treatment actually being received, analyzed according to the treatment group allocated by randomization.
PP	The PP population is a subset of ITT population with no major protocol deviations. Participants included in this population will fulfill at least the criteria below: • randomized and received only the treatment allocated at the randomization • did not permanently discontinue treatment The PP population will be fully defined in the SAP.
Safety	All randomized participants who received at least one dose of IMP, regardless of the amount of treatment administered. Patients will be analyzed according to the treatment actually received.

ICF: informed consent form; IRT: interactive response technology; ITT: intent to treat; PP: per protocol; SAP: statistical analysis plan

9.4 STATISTICAL ANALYSES

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy analyses

All efficacy analyses will be performed on the ITT population. Sensitivity analyses will be performed on the PP population on a selection of endpoints.

Table 7 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary: Percent time in glucose range of ≥70 to ≤180 mg/dL (≥3.9 to ≤10 mmol/L) at Week 12, obtained using CGM	Primary endpoint using available data from the 12-week randomized period will be analyzed using an ANCOVA model including the fixed categorical effects of treatment group (Toujeo, Tresiba), randomization stratum of screening HbA1c (<8.0% versus ≥8.0%), as well as, the continuous fixed covariate of baseline percent time in range value. This procedure will provide baseline adjusted least-squares means estimates at Week 12 for both treatment groups, as well as, the differences of these estimates, with their corresponding standard errors (SEs) and 95% CIs. To assess non-inferiority, the lower bound of the two-sided 95% CI for the adjusted difference estimate of m1 - 0.9*m0 at Week 12 will be compared to 0. Non-inferiority will be demonstrated if the lower bound of the two-sided 95% CI of the adjusted difference estimate of m1 - 0.9*m0 at Week 12 on the ITT population is >0. A sensitivity analysis will be performed using the PP population. Let m1 and m0 be the true means for the Toujeo and Tresiba groups, respectively. To assess non-inferiority, the lower bound of the two-sided 95% CI for the adjusted difference estimate of m1 - 0.9*m0 at Week 12 will be compared to 0. Non-inferiority will be demonstrated if the lower bound of the two-sided 95% CI of the adjusted difference estimate of m1 - 0.9*m0 at Week 12 on the ITT population is >0. A sensitivity analysis will be performed using the PP population.
Secondary: CGM endpoints at Week 12 (see Section 3)	CGM endpoints will be analyzed using the same model as described for the primary endpoint using the ITT population. Exploratory analysis will be performed on within day glucose CV to summarize the treatment effects across subgroup defined by within day CV<36% vs. >=36% at baseline.
Secondary	
• Change from baseline to Week 12 in HbA1c	Change in HbA1c will be analyzed using an analysis of covariance (ANCOVA) model including fixed categorigal effect of treatment group (Toujeo, Tresiba), as well as, the continuous fixed covariate of baseline HbA1c value.
• Change from baseline to Week 12 in central lab FPG	Change in FPG will be analyzed using ANCOVA model including the randomization stratum of HbA1c at screening (<8.0%, ≥8.0%), treatment group (Toujeo, Tresiba), as well as, the continuous fixed covariate of baseline FPG value.
Exploratory	[Will be described in the statistical analysis plan finalized before database lock]

To control the type I error, a hierarchical step-down testing procedure described by Hochberg and Tamhane (3) will be applied for the primary efficacy endpoint and the main secondary endpoint:

- Step 1 proceeds to assess non-inferiority of Toujeo versus Tresiba on the percent time in range in 70-180 mg/dl.
- Step 2: only if step 1 is demonstrated, then non-inferiority of Toujeo versus Tresiba on the glucose total CV will be tested with a relative non-inferiority margin of 10%.
- Step 3: only if step 2 is demonstrated, then difference between Toujeo and Tresiba on the percent time in range in 70-180 mg/dl will be tested.

No multiplicity adjustment will be made on other secondary/other efficacy variables; 95% CI and P-values presented for these endpoints will be done for descriptive purpose only.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety Population.

The summary of safety results will be presented by treatment group.

The baseline value is defined generally as the last available value before randomization.

For all safety data, the observation period will be divided as follows:

- The **pre-treatment** phase is defined as the time from when the patients sign the informed consent to randomization.
- The **on-treatment** phase is defined as the time from the first injection of the open label IMP (included) up to 2 days after the last injection of IMP.
- The **post-treatment** phase is defined as the time after the on-treatment phase until the end of the study (Follow up Visit).

Treatment-emergent AEs (TEAEs) are AEs that developed or worsened or became serious during the on-treatment phase.

Table 8 - Safety analyses

Endpoint	Statistical Analysis Methods
Secondary:	
• Number of participants with AEs	TEAEs, treatment-emergent SAEs, TEAEs leading to death, and TEAEs leading to treatment discontinuation will be summarized by treatment group for the 12-week on-treatment period. All adverse events will be coded to a “preferred term” (PT) and “high-level group term” (HLGT), “high level term” (HLT) and associated primary “system organ class” (SOC) using the version of MedDRA currently in use by the Sponsor at the time of database lock. Adverse event incidence tables will present by SOC (sorted by internationally agreed order), HLGT, HLT and PT sorted in alphabetical order, and for each treatment group, the number (n) and percentage (%) of patients experiencing at least one AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment period. The denominator for computation of percentages is the safety population within treatment group.
• Number of participants with at least one hypoglycemic event from baseline to Week 12	The number and incidence of patients experiencing at least one hypoglycemic event will be presented per treatment group and type of hypoglycemic event (see Section 8.2.4) and according to time of occurrence (nocturnal [ie, 00:00 to 05:59], any time of day and daytime [ie, 06:00 to 23:59]) during the 12-week on treatment period. The Odds Ratio and its corresponding 95% CI of Toujeo arm over Tresiba arm for each hypoglycemic event (nocturnal and any time of the day) will be estimated by a logistic regression model.
• Number of hypoglycemic events per participant year from baseline to Week 12.	The rate of hypoglycemic events (in patient-year of exposure) will be determined per treatment group and type of hypoglycemic event (see Section 8.2.4), and according to time of occurrence (nocturnal [ie, 00:00 to 05:59], any time of the day) during the 12-week on treatment period.
Exploratory	Not applicable

9.4.3 Other analyses

Not applicable.

9.5 INTERIM ANALYSES

No interim analysis is planned during the study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
  - Applicable ICH Good Clinical Practice (GCP) Guidelines,
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC,
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures,
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

10.1.3 Data Protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation).

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.4 Committees Structure

The steering committee is composed of scientists with clinical and methodological expertise in diabetes and conduct of clinical trials. This committee, led by a chairman, is responsible for producing and conducting a scientifically sound study and for ensuring accurate reporting of the study. In that capacity, the steering committee must address scientific issues encountered during the study.

10.1.5 Dissemination of Clinical Study Data

Sanofi shares information about clinical trials and results on publically accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8 Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

10.1.9 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The tests detailed in Table 9 will be performed by the central laboratory.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 9 - Protocol-required laboratory assessments

Laboratory assessments	Parameters			
Hematology	Platelet count Red blood cell (RBC) count	Hemoglobin Hematocrit	White blood cell (WBC) count	
Clinical chemistry	Uric acid	Potassium	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)	Total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin)
	Creatinine	Sodium	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)	Estimated creatinine clearance
	FPG HbA1c	Blood urea nitrogen (BUN)	Alkaline phosphatase	
Other screening tests	• C peptide • Serum human chorionic gonadotropin (hCG) pregnancy test (for women of childbearing potential at screening) • Urine hCG pregnancy test for WOCBP at Visit-6 and 18 (to be confirmed with serum test if positive)			

The results of central laboratory tests will be uploaded to the clinical database. Investigators will receive the reports from central laboratory and must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - 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.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor’s representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor’s representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor’s representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor’s representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAES

SAE reporting to the Sponsor's representative via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in a separate document.

SAE reporting to the Sponsor's representative via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in a separate document.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy,
   - Documented bilateral salpingectomy,
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required,
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE

Female participants

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
ACCEPTABLE METHODS[d]
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[e]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. e) Male condom and female condom should not be used together (due to risk of failure with friction).

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

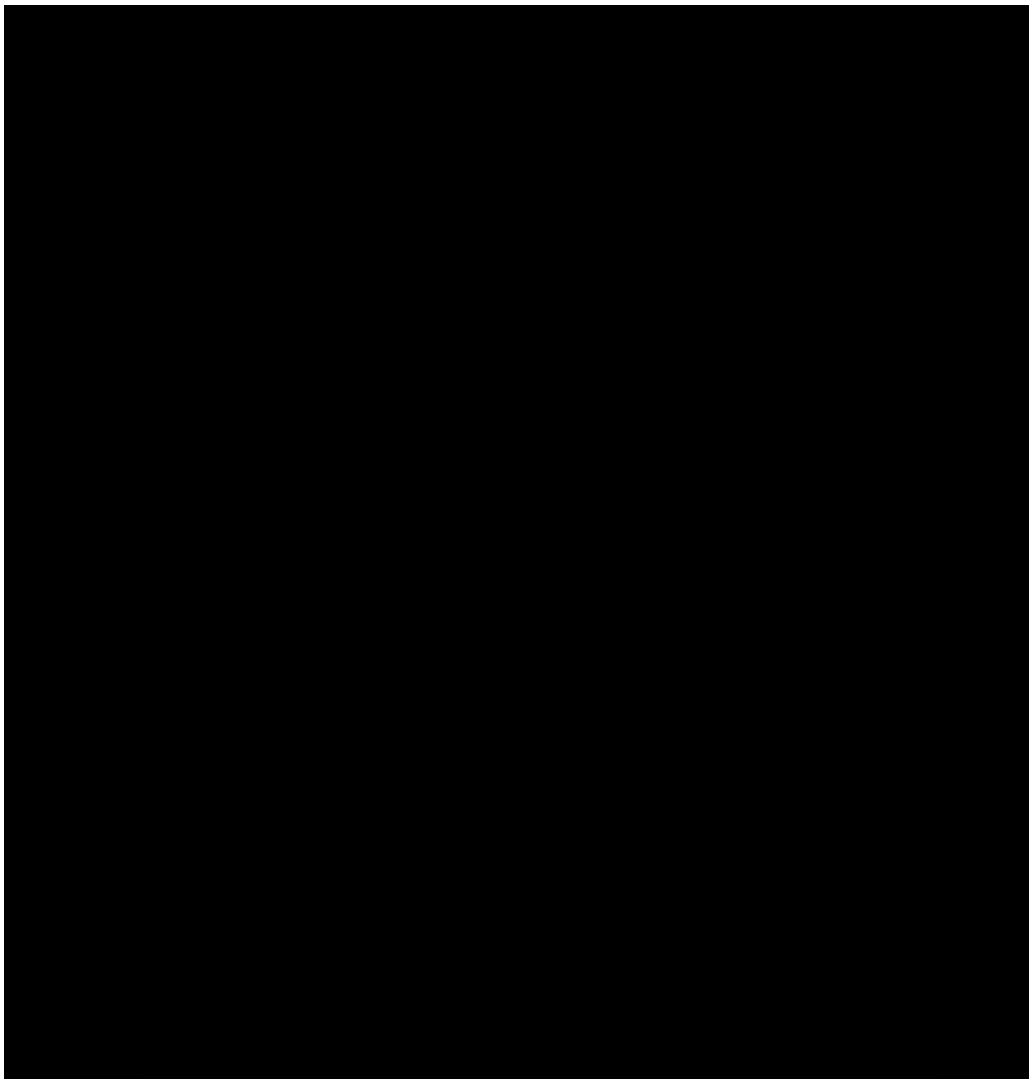
  Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 APPENDIX 5: QUESTIONNAIRE

10.5.1 The Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs)

DTSQs © Prof Clare Bradley 9/93. English for UK and USA (rev. 7/94)
Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK.

10.5.2 The Diabetes Treatment Satisfaction Questionnaire Change Version



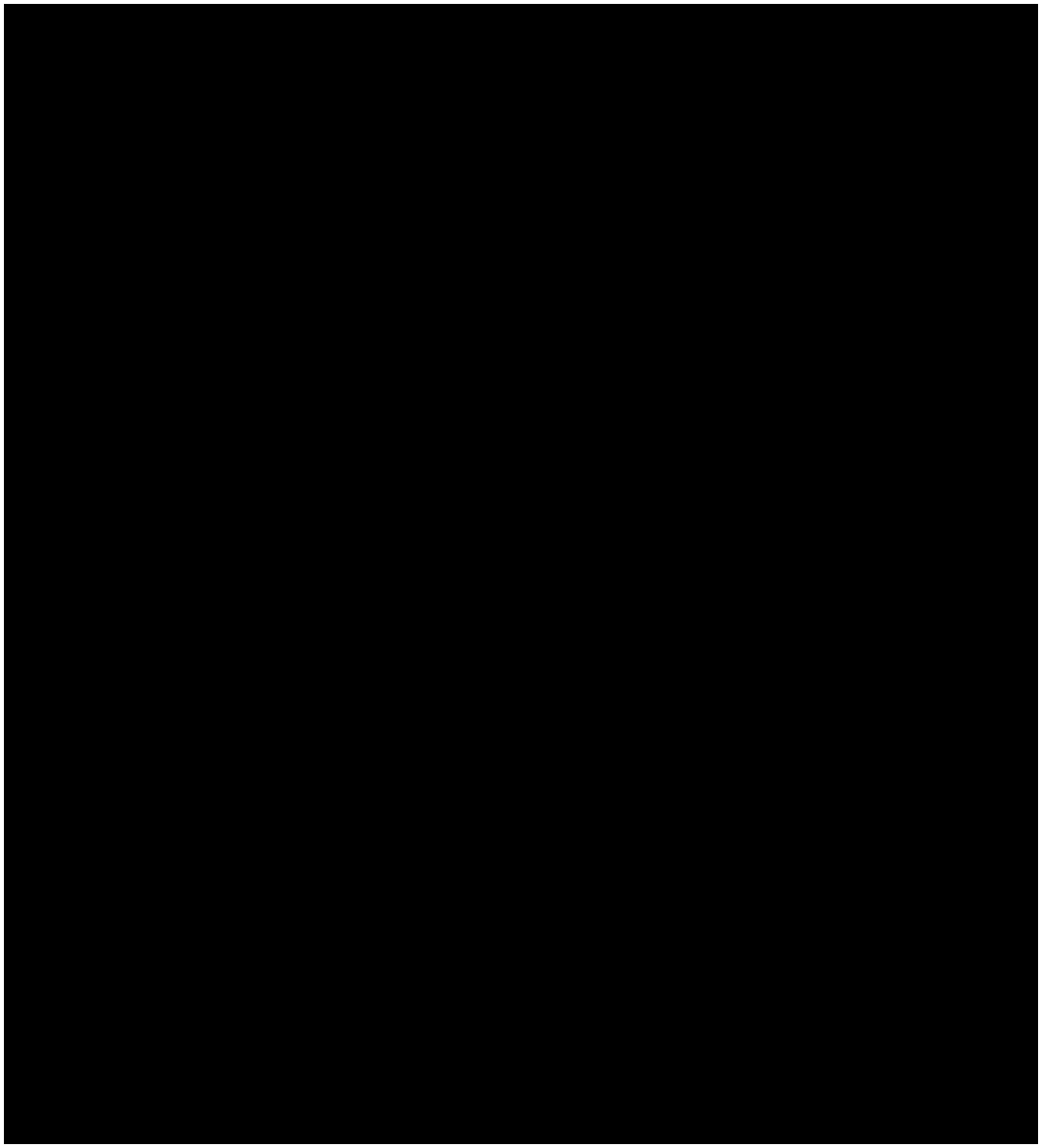
NOT FOR USE: for review by sanofi-aventis, ref HPR1649
DTSQc © Prof Clare Bradley 11.9.96 Standard UK English (rev. 4.3.98; generic intro. rev. 28.2.02)
Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK

10.5.3 MOS Sleep

Copyright, 1986, RAND.
MOS 12-Item Sleep Scale Acute – Revised 2010
United States (English)

Copyright, 1986, RAND.
MOS 12-Item Sleep Scale Acute – Revised 2010
United States (English)

10.5.4 WPAI



WPAI:SHP V2.0 (US English)

Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment measure. Pharmacoeconomics 1993; 4(5):353-365.

2

10.6 APPENDIX 6: ADA HYPOGLYCEMIA DEFINITIONS

In this study, hypoglycemia is categorized according to the American Diabetes Association workgroup on hypoglycemia classification:

- Defining and Reporting Hypoglycemia in Diabetes: A Report from American diabetes Association Workgroup on hypoglycemia Diabetes Care. 2005 May;28(5):1245-9.
- Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care. 2013;36(5):1384-95.

In addition to the threshold of ≤70 mg/dL (≤3.9 mmol/L), hypoglycemia episodes with a plasma glucose of <54 mg/dL (<3.0 mmol/L) will be analyzed separately:

International Hypoglycemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017; 40(1): 155-157.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.8 APPENDIX 8: ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ANCOVA:	analysis of covariance
CGM:	continuous glucose monitoring
CI:	confidence interval
CV:	coefficient of variation
DCCT:	Diabetes Control and Complications Trial
eCRF:	electronic case report form
FPG:	fasting plasma glucose
GIR:	glucose infusion rate
HbA1c:	glycated hemoglobin A1c
IMP:	investigational medicinal product
IRT:	interactive response technology
ITT:	intent to treat
PD:	Pharmacodynamics
PK:	Pharmacokinetics
SAE:	serious adverse event
SC:	subcutaneous
SD:	standard deviation
SE:	standard errors
SMPG:	self-monitoring of plasma glucose
T1DM:	type 1 diabetes mellitus

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Signature Page for VV-CLIN-0514702 v2.0
lps14947-16-1-1-protocol

Approve & eSign	[redacted]
Approve & eSign	