

CLINICAL TRIAL PROTOCOL

TITLE: A 24-week, Multicenter, Randomized, Open-label, Parallel-group Study Comparing the Efficacy and Safety of Toujeo® and Tresiba® in Insulin-Naive Patients with Type 2 Diabetes Mellitus not Adequately Controlled with Oral Antidiabetic Drug(s) ± GLP-1 receptor agonist

COMPOUND: Toujeo®/Insulin Glargine 300 U/mL/HOE901

STUDY NUMBER: LPS14584

STUDY NAME: NA

NCT02738151

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CLINICAL TRIAL SUMMARY

COMPOUND: Toujeo®/Insulin Glargine 300 U/mL/HOE901	STUDY No: LPS14584
TITLE	A 24-week, multicenter, randomized, open-label, parallel-group study comparing the efficacy and safety of Toujeo® and Tresiba® in insulin-naïve patients with type 2 Diabetes Mellitus not adequately controlled with Oral Antidiabetic Drug(s) ± GLP-1 receptor agonist
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	4
STUDY OBJECTIVE(S)	<p>Primary objective:</p> <p>To demonstrate non-inferiority in the efficacy of Toujeo in comparison with Tresiba in terms of change of glycated hemoglobin A1c (HbA1c) from baseline to Week 24 in insulin-naïve patients with Type 2 Diabetes mellitus (T2DM) not adequately controlled with Oral Antidiabetic Drugs (OADs) with or without GLP-1 receptor agonist.</p> <p>Secondary objective(s):</p> <p>To assess the effects of Toujeo in comparison with Tresiba on:</p> <ul style="list-style-type: none"> • Change in HbA1c over Week 12, • Change in Fasting plasma glucose (FPG) over Week 12 and Week 24, • Change of Fasting Self-Monitored Plasma Glucose (SMPG) and 4-point and 8-point SMPG profile over Week 12 and Week 24, • Change of mean 24-hour plasma glucose over Week 12 and Week 24, • Change in variability of fasting SMPG and 24-hour plasma glucose over Week 12 and Week 24, • Percentage of patients reaching HbA1c targets <7% and ≤ 6.5% at Week 12 and Week 24, • Percentage of patients reaching HbA1c targets <7% and ≤ 6.5% at Week 12 and Week 24 without severe and/or confirmed hypoglycemia during the 12 week and 24-week treatment period, • Percentage of patients requiring rescue therapy during the 24-week treatment period. <p>To assess the frequency of occurrence and diurnal distribution of hypoglycemia by category of hypoglycemia (symptomatic, asymptomatic, nocturnal, severe, probable and pseudo).</p> <p>To assess the safety in each treatment group over 24 weeks of treatment.</p> <p>To assess the treatment effects in each treatment group on Patient Reported Outcomes (PROs) measured by the following questionnaires:</p> <ul style="list-style-type: none"> • Diabetes Treatment Satisfaction Questionnaire (DTSQ, status version and change version), • Hypoglycemia Attitude and Behavior Scale (HABS).

STUDY DESIGN	<p>A 24 weeks, multinational, multicenter, randomized, open-label, 2-arm parallel-group trial. Patients will receive in a 1:1 ratio either Toujeo or Tresiba.</p> <p>Randomization will be stratified by value of HbA1c obtained at the screening visit (<8.0%; ≥8.0%) and sulphonylurea (SU) or meglitinides use before the day of screening (Yes; No).</p>
STUDY POPULATION Main selection criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Adult patients with T2DM inadequately controlled with OADs therapy with/without GLP-1 receptor agonist at stable dose for at least 3 months, • Signed written informed consent. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Age <18 years at time of informed consent, • HbA1c <7.5% or >10.5% (at screening visit), • BMI <25 kg/m² or >40 kg/m², • History of T2DM for less than 1 year before screening, • Less than 6 months before screening on OADs treatment and GLP-1 receptor agonist (if taken), • Current or previous insulin use except for a maximum of 8 consecutive days or totally 15 days (eg, acute illness, surgery) during the last year prior to screening, • Initiation of new glucose-lowering medications and/or weight loss drug in the last 3 months before screening visit, • Patient receiving only non-insulin antidiabetic drugs not approved for combination with insulin according to local labelling/ local treatment guideline, • History of hypoglycemia unawareness or repeated episodes of severe hypoglycemia or metabolic acidosis, including hospitalization for diabetic ketoacidosis during the last 12 months prior to screening, • Unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema likely to require treatment (eg, laser, surgical treatment or injectable drugs) during the study period, • End stage renal disease (defined as estimated GFR (MDRD) <15 ml/min/1.73 m² or being on hemodialysis), • Any acute or chronic condition that in the opinion of investigator would affect the patient safety, compliance or study results, • Any contraindication to use of Toujeo or Tresiba as defined in the national product label, hypersensitivity to Toujeo or Tresiba active ingredients or one of the excipients, • Pregnant or breast-feeding women.

Total expected number of patients	Approximately 920 patients (Toujeo: n = 460; Tresiba: n = 460)
STUDY TREATMENT(s)	
Investigational medicinal product(s) Formulation: Route(s) of administration:	<p>Tested drug: Toujeo (insulin glargine 300 U/mL)</p> <p>Toujeo will be supplied as a sterile, non-pyrogenic, clear, colorless solution in the Toujeo SoloStar prefilled (disposable) pen (insulin glargine 300 units/mL solution for subcutaneous (SC) injection). Each Toujeo® SoloStar® contains in total 450 units of insulin glargine (1.5 mL of 300 units/mL insulin glargine solution). This pen allows dose setting in the range of 1–80 units with minimum of 1 unit increment. Mixing of Toujeo with other insulin products is not allowed nor dilution.</p> <p>Control drug: Tresiba® (insulin Degludec 100 U/mL)</p> <p>Tresiba® will be supplied as a sterile, non-pyrogenic, clear, colorless solution in the marketed Tresiba® FlexTouch prefilled (disposable) pen (insulin degludec 100 units/mL solution for SC injection).</p> <p>Each Tresiba FlexTouch contains in total 300 units of insulin degludec (3.0 mL of 100 units/mL insulin degludec solutions). This pen allows dose setting in the range of 1–80 units with minimum of 1 unit increment.</p> <p>Mixing of Tresiba with other insulin products is not allowed nor dilution.</p> <p>Toujeo and Tresiba will be self-administered by SC injections once daily between 6:00 PM and 8:00 PM throughout the study treatment period.</p>
Dose regimen:	<p>Starting dose:</p> <p>The recommended daily starting dose of each basal insulin is defined per label with once daily as below followed by individual dose adjustment:</p> <ul style="list-style-type: none"> • Toujeo: 0.2 units/kg • Tresiba: 10 units <p>Dose adjustment</p> <p>During the study, doses of either basal insulin, Toujeo or Tresiba will be titrated to achieve glycemic targets without hypoglycemia according to the same algorithm as below.</p> <ul style="list-style-type: none"> • After randomization, 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 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia episodes. • Thereafter, until the end of the study, the dose will be adjusted as necessary to maintain this fasting SMPG target. • Dose adjustments are based on a median of fasting SMPG values from the last 3 measurements, which includes the value measured on the day of titration, measured by the patient using glucometers and accessories supplied by the sponsor. <p>The best efforts should be made to reach the target glucose by 8-12 weeks after randomization.</p>

	<p>Table 1 - Dose adjustment algorithm</p> <table> <tr> <th>Median# Fasting SMPG from last 3 measurement (mg/dL)</th><th>Toujeo and Tresiba dose change*</th></tr> <tr> <td>>140 (>7.8 mmol/L)</td><td>+ 6 U</td></tr> <tr> <td>>120 and ≤140 (>6.7 - ≤7.8 mmol/L)</td><td>+ 4 U</td></tr> <tr> <td>>100 and ≤120 (>5.6 - ≤6.7 mmol/L)</td><td>+ 2 U</td></tr> <tr> <td>≥80 and ≤100 (≥4.4 - ≤5.6 mmol/L)</td><td>No change</td></tr> <tr> <td><80 (<4.4 mmol/L) or occurrence of 1 symptomatic confirmed hypoglycemia episode documented in the preceding week</td><td>-2U or at the discretion of the investigator</td></tr> </table> <p>* Dose adjustment should not be more often than every 3 days.</p> <p># 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).</p>	Median# Fasting SMPG from last 3 measurement (mg/dL)	Toujeo and Tresiba dose change*	>140 (>7.8 mmol/L)	+ 6 U	>120 and ≤140 (>6.7 - ≤7.8 mmol/L)	+ 4 U	>100 and ≤120 (>5.6 - ≤6.7 mmol/L)	+ 2 U	≥80 and ≤100 (≥4.4 - ≤5.6 mmol/L)	No change	<80 (<4.4 mmol/L) or occurrence of 1 symptomatic confirmed hypoglycemia episode documented in the preceding week	-2U or at the discretion of the investigator
Median# Fasting SMPG from last 3 measurement (mg/dL)	Toujeo and Tresiba dose change*												
>140 (>7.8 mmol/L)	+ 6 U												
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>100 and ≤120 (>5.6 - ≤6.7 mmol/L)	+ 2 U												
≥80 and ≤100 (≥4.4 - ≤5.6 mmol/L)	No change												
<80 (<4.4 mmol/L) or occurrence of 1 symptomatic confirmed hypoglycemia episode documented in the preceding week	-2U or at the discretion of the investigator												
<p>Noninvestigational medicinal product(s) (if applicable)</p> <p>Formulation:</p> <p>Route(s) of administration:</p> <p>Dose regimen:</p>	<p>Background therapy: OADs and GLP-1 receptor agonist (if taken) will be considered as NIMP(s).</p> <p>Rescue medication will be considered as NIMP(s): anti-diabetic medication (should be based on Investigator's decision and local labeling documents).</p> <p>OADs: Oral administration</p> <p>GLP-1 receptor agonist (if taken): SC injection</p> <p>The type and dose of anti-diabetic background therapy will remain unchanged during the study; unless agents not approved in combination with insulin according to local labeling/local treatment guideline or identified safety concerns necessitate a reduction in dose or discontinuation of non-insulin antidiabetic drug(s).</p> <p>Rescue therapy:</p> <p>Routine fasting SMPG, central laboratory FPG measurements and central laboratory alerts on HbA1c are set up to ensure that glycemic parameters remain under predefined threshold values. The threshold values for rescue are defined as follows:</p> <p>From Visit 14 (Week 12): FPG >200 mg/dL (11 mmol/L) and / or HbA1c>8.5%.</p> <p>In case of FPG or HbA1c above the target values and/or SMPG are not improving as expected in spite of successive IMP dose titration (note: the investigator should ensure that no reasonable explanation exists for insufficient glucose control and undertake appropriate action to decrease FPG/HbA1c under the threshold values), intensification of the treatment is to be considered.</p> <p>The choice of the anti-diabetic treatment to be added to the basal insulin should be based on Investigator's decision and local labeling documents, adding prandial insulin may be the preferred option. The addition of a new antidiabetic drug or increase in dose of background antidiabetic medication ("rescue") should not be decided based on a single FPG or HbA1c value but be based on a thorough evaluation of the patient's glycemic control.</p>												

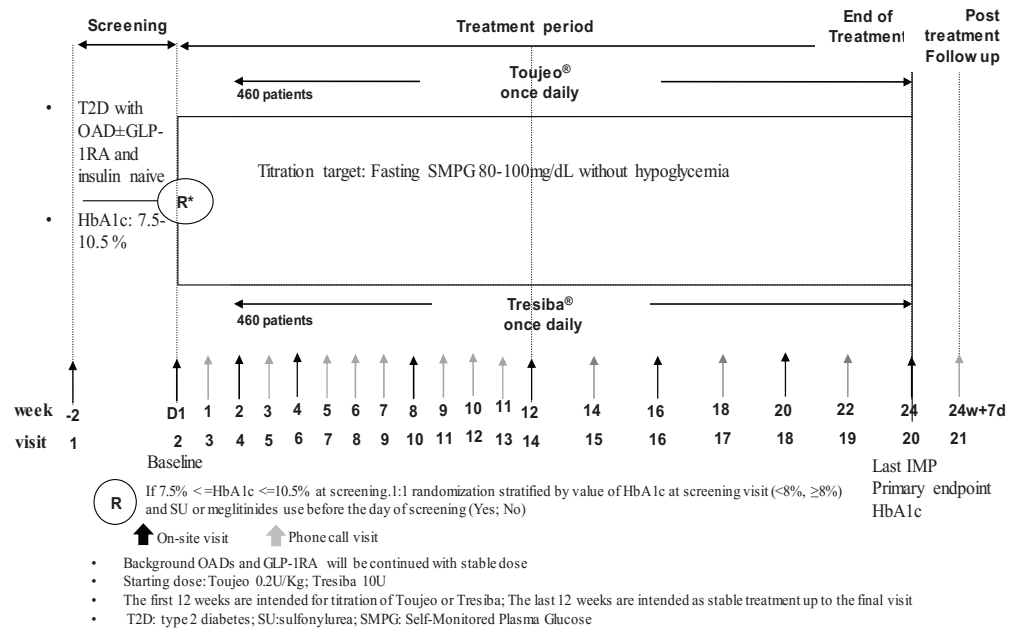
	<p>The type of rescue therapy, reason for initiating rescue therapy and the day of starting rescue therapy along with the dose will be documented.</p> <p>All assessments for primary and secondary efficacy and safety parameters planned in final on treatment assessment visit (Visit 20) should be performed before starting the “rescue medication” (adding new antidiabetic agent or increase in dose of existing background antidiabetic medication.)</p> <p>Then the patient continues the IMP and stays in the study in order to collect safety information.</p>
ENDPOINT(S)	<p>Primary endpoint:</p> <p>HbA1c (change from baseline to endpoint [Week 24])</p> <p>Secondary endpoint(s):</p> <p>Secondary efficacy endpoints</p> <ul style="list-style-type: none"> • HbA1c: change from baseline to Week 12 • FPG: change from baseline to Week 12 and Week 24 • Fasting SMPG: change from baseline to Week 12 and Week 24, • Change in 4-point and 8-point SMPG profiles per time-point from baseline to Week 12 and Week 24, • Change of mean 24-hour plasma glucose based on 8-point SMPG from baseline to Week 12 and Week 24, • Change in variability of fasting SMPG and 24-hour plasma glucose based on 8-point SMPG from baseline to Week 12 and Week 24, • Percentage (%) of patients reaching target HbA1c <7% and ≤6.5% at Week 12 and Week 24; • Percentage (%) of patients reaching target HbA1c <7% and ≤6.5% at Week 12 and Week 24 without severe and/or confirmed hypoglycemia (70 mg/dL and 54 mg/dL as cut off point) event during the 12-week and 24-week treatment period, • Percentage (%) of patients with SU or meglitinide dose reduction/discontinuation due to hypoglycemia during 24 weeks treatment period, • Percentage of patients requiring rescue therapy during 24 weeks treatment period, • Basal insulin dose (U and U/kg body weight): change from baseline to Week 12 and Week 24. <p>Safety endpoint:</p> <p>Safety analyses will be based on all hypoglycemia events, local tolerability at injection site, hypersensitivity reactions, other adverse events (AE) or serious adverse events (SAE) including Adverse events with special interest (AESI) and other safety information including vital signs, body weight.</p> <p>Hypoglycemia will be classified as ADA category and analyzed using the following variables:</p> <ul style="list-style-type: none"> • Percentage of patients with at least one episode of confirmed hypoglycemia (cut off value 70 or 54 mg/dL) and event rate during

	<p>24 weeks treatment periods,</p> <ul style="list-style-type: none"> • Rate of hypoglycemia per month computed as: $365.25/12 \times (\text{number of episodes of hypoglycemia})/(\text{number of days exposed in time window})$, • Percentage of patients and event rate of Hypoglycemia by study period (for ≤ 12 weeks, for >12 weeks to ≤ 24 weeks) to evaluate the potentially increased risk of hypoglycemia during the initial 12-week after starting treatment with basal insulin, • The diurnal distribution of the occurrence of each episode of documented hypoglycemia by category will be presented by two-hour timeframe over 24 hours during the 24 weeks treatment period. <p>Other endpoint(s):</p> <ul style="list-style-type: none"> • Patient reported outcome (PRO): <ul style="list-style-type: none"> ○ Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) and change version (DTSQc). ○ Hypoglycemia Attitudes and Behavior Scale (HABS)
ASSESSMENT SCHEDULE	<p>The schedule of study-related procedures/assessments is detailed in the Study Flowchart</p> <p>Early termination:</p> <p>For all patients who prematurely and permanently discontinue the study treatment, assessments scheduled at the “End of treatment visit” and the “Post-treatment safety follow up visit”, will be performed as soon as possible. Afterward, the patients should continue in the study up to the scheduled date of study completion.</p>
STATISTICAL CONSIDERATIONS	<p>Sample size determination:</p> <p>Number of subjects: N=920</p> <p>A sample size of 920 patients (460 with Toujeo and 460 with Tresiba) will ensure that the upper confidence limit of the two-sided 95% CI for the adjusted mean difference between Toujeo and Tresiba would not exceed 0.3% HbA1c with 90 % power assuming that standard deviation (SD) is 1.4%, and that the true difference between Toujeo and Tresiba is zero in HbA1c.</p> <p>General aspects of the analyses:</p> <p>For efficacy analyses, the baseline for both treatment groups is defined as the last available value prior to randomization.</p> <p>Analysis population:</p> <p>The primary efficacy population will be the ITT (intent-to-treat) population, which includes all randomized patients who received at least one dose of IMP, irrespective of the treatment actually being received, analyzed according to the treatment group allocated by randomization.</p> <p>The safety population is defined as all randomized patients 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.</p> <p>Primary analysis:</p> <p>The primary efficacy endpoint (change in HbA1c from baseline to endpoint [Week 24]) using available data during the 24-week on-treatment period will be analyzed using a mixed-effect model with repeated measures (MMRM)</p>

	<p>approach, using the missing at random framework carried out via SAS PROC MIXED using adequate contrasts. The model will include fixed categorical effects of treatment group, visit, treatment-by-visit interaction, randomization stratum of use of SU or meglitinide at screening (Yes versus No) and the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction.</p> <p>A stepwise closed testing approach will be used for the primary efficacy variable to assess non-inferiority and superiority sequentially.</p> <ul style="list-style-type: none"> Step 1 will proceed to assess non-inferiority Toujeo versus Tresiba. <p>To assess non-inferiority, the upper bound of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to Week 24 between Toujeo and Tresiba will be compared with the predefined non-inferiority margin of 0.3% HbA1c. Non-inferiority will be demonstrated if the upper bound of the two-sided 95% CI of the difference between Toujeo and Tresiba on ITT population is <0.3%.</p> <ul style="list-style-type: none"> Step 2 will test superiority of Toujeo over Tresiba, only if non-inferiority of Toujeo versus Tresiba has been demonstrated. <p>The superiority of Toujeo over Tresiba will be demonstrated if the upper bound of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to Week 24 between Toujeo over Tresiba on ITT population is <0 (zero).</p> <p>Analysis of secondary endpoints:</p> <p>All secondary efficacy endpoints will be analyzed or summarized on the 24-week on treatment period using the ITT population.</p> <p>Safety analyses will be descriptive, based on the safety population.</p>
DURATION OF STUDY PERIOD (per patient)	<p>The study consists of:</p> <ul style="list-style-type: none"> Up-to 2 weeks screening period; it can be exceptionally extended up to one additional week, A 24-week open label comparative efficacy and safety treatment period, A 7-day post-treatment safety follow-up period for all the patients after permanent investigational medical product(IMP) discontinuation(except for patients who prematurely discontinue the study treatment but continue in the study) <p>In total the maximum study duration will be approximately 27 weeks per patient:</p> <p>2 weeks + 24 weeks ± 5 days + 7 days</p>

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

	Screening	Treatment period																			Post-treatment observations
VISIT	1 ^a	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Visit 3-9: ± 3 days / vs. baseline Visit 10-20: ± 5 days/ vs. baseline Visit 21: -1~+3 days vs. visit 20	Wk-2	D1 baseline	Wk1 ☎ ^b	Wk2	Wk3 ☎ ^b	Wk4	Wk5 ☎ ^b	Wk6 ☎ ^b	Wk7 ☎ ^b	Wk8	Wk9 ☎ ^b	Wk10 ☎ ^b	Wk11 ☎ ^b	Wk12	Wk14 ☎ ^b	Wk16	Wk18 ☎ ^b	Wk20	Wk22 ☎ ^b	Wk24 end of treatment	V20+7days ☎ ^b End of study
Informed Consent	X																				
Inclusion/Exclusion Criteria	X	X																			
Demography, medical history; diabetes history, prior medications	X																				
Physical examination	X	X																		X	
Height	X																				
Body weight	X	X		X		X				X				X		X		X		X	
Dispensation of glucometer	X																				
Dispensation diary	X	X		X		X				X				X		X		X			
Training of glucometer and diary and SMPG profile ^c	X	X																			
Collection of diary		X		X		X				X				X		X		X		X	
Collection of glucose meter (if mandatory by local regulation)																				X	
Diet and lifestyle counseling	Provided at on site visit if needed throughout the study																				
Randomization		X																			
IVRS/IWRS call	X	X				X				X				X		X		X		X	

	Screening	Treatment period																			Post-treatment observations
VISIT	1 ^a	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Visit 3-9: ± 3 days / vs. baseline Visit 10-20: ± 5 days/ vs. baseline Visit 21: -1~+3 days vs. visit 20	Wk-2	D1 baseline	Wk1 ☎ ^b	Wk2	Wk3 ☎ ^b	Wk4	Wk5 ☎ ^b	Wk6 ☎ ^b	Wk7 ☎ ^b	Wk8	Wk9 ☎ ^b	Wk10 ☎ ^b	Wk11 ☎ ^b	Wk12	Wk14 ☎ ^b	Wk16	Wk18 ☎ ^b	Wk20	Wk22 ☎ ^b	Wk24 end of treatment	V20+7days ☎ ^b End of study
Treatment																					
Pre-filled disposable pen (SoloStar® or FlexTouch®) and self-injection training ^c		X																			
Dispensation of Study medication		X				X				X				X		X		X			
Counting / collecting used and unused study medication ^d				X		X				X				X		X		X		X	
Compliance Check (Review of diary)		X		X		X				X				X		X		X		X	
Documentation of the IMP dose		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication including antihyperglycemic medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy																					
Fasting condition visit ^e	X	X								X				X						X	
HbA1c (central lab)	X	X								X				X						X	
Fasting plasma glucose (central lab)		X								X				X						X	
SMPG ^f		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
4-point SMPG ^f						X				X											
8-point SMPG ^f		X												X						X	
DTSQs (status version) ^g HABS		X												X						X	
DTSQc (change version) ^g														X						X	

	Screening	Treatment period																			Post-treatment observations	
VISIT	1 ^a	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit 3-9: ± 3 days / vs. baseline Visit 10-20: ± 5 days/ vs. baseline Visit 21: -1~+3 days vs. visit 20	Wk-2	D1 baseline	Wk1 ☎ ^b	Wk2	Wk3 ☎ ^b	Wk4	Wk5 ☎ ^b	Wk6 ☎ ^b	Wk7 ☎ ^b	Wk8	Wk9 ☎ ^b	Wk10 ☎ ^b	Wk11 ☎ ^b	Wk12	Wk14 ☎ ^b	Wk16	Wk18 ☎ ^b	Wk20	Wk22 ☎ ^b	Wk24 end of treatment	V20+7days ☎ ^b End of study	
Safety																						
AE/SAE/Hypoglycemia/ injection site reaction	Continuously assessed and recorded all along the study(report SAE/AESI to the sponsor within 24 hours)																					
Vital signs ^h	X	X		X		X				X				X		X		X		X		
12-lead ECG	X																					
Hematology ⁱ , Clinical Chemistry(central lab) ^j	X																					
Urine analysis(central lab) ^k	X																					
Serum FSH and estradiol (Menopausal women only(central lab))	X																					
Pregnancy test (WOCBP only) ^l	x	x																		x		
Rescue therapy			All assessments planned in V20 should be performed before starting rescue therapy, patients then continue the study treatment (including background therapy), and all visits and assessments should be performed as scheduled;																			
Prematurely permanent IMP discontinuation			Patients should have a visit as soon as possible with the assessments normally planned in V20. Afterward, the patients should continue in the study up to the scheduled date of study completion. They should be followed up according to the study procedures as specified in the protocol (except for the 7-day safety post-treatment follow-up).																			

- a If any of the laboratory parameters are not available upon the end of the screening period (eg, sample material damaged during transport etc) a retest can be performed. If this is the case (and exceptionally in other situations if justified) the screening period can be extended of one additional week, ie, baseline visit (V2, Day 1) can be scheduled no later than 3 weeks after screening visit (V1, Week -2)
- b Mandatory telephone visit or optional clinical visit. During up-titration, until a stable basal insulin dose is achieved, as well as throughout the later course of the study, additional contacts (phone, on-site visit) will be made available for patients to discuss dose adjustments in-between the scheduled visits. The frequency of the contacts is at the discretion of the investigator and will be determined by the needs of the patient
- c Training repeated as often as necessary
- d Visit 4: collecting used study medication only.
- e Fasting condition: patient to come after a fasting period of at least 8 hours: during this time, no food or liquid intake other than water.
- f Self-monitored plasma glucose (SMPG):
Fasting pre-breakfast SMPG: test and collected daily until up-titration has been completed and fasting pre-breakfast SMPG is stable in the target range. Thereafter, fasting pre-breakfast SMPG are mandatory on at least 3 days per week. On the day of 4-point blood glucose profile performed, fasting SMPG will be considered as the first point of measurement, ie, pre-breakfast time point.
4-point **blood glucose profiles** (pre-breakfast, pre-lunch, pre-dinner and bedtime): on at least one day in the 5 days before Week 4 and Week 8 on site visit.
8-point **blood glucose profiles** (03:00 at night, before and 2 hours after breakfast, before and 2 hours after lunch, before and 2 hours after dinner, at bedtime): on at least one day in the 5 days before the baseline visit and before Week 12 and Week 24 on site visit. Special attention should be paid that the 3:00 AM. SMPG value is recorded.
SMPG in case of hypoglycemic symptoms: whenever experienced (prior to countermeasure if possible).
- g DTSQs and HABS are tested at baseline, Week 12 and Week 24. DTSQc is only tested at Week 12 and Week 24. At 12 and 24 weeks, DTSQs will be administered before the DTSQc.
- h Heart rate, blood pressure in sitting condition on reference arm. At screening visit (V1) only: additionally determination of the reference arm for blood pressure measurements during the study (in sitting condition).
- i Hematology: Erythrocytes, hemoglobin, hematocrit, leukocytes and platelets.
- j Clinical chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), AST, ALT, ALP, creatinine, estimated GFR (MDRD), sodium, potassium.
- k Urine analysis: pH, glucose, ketones, leucocytes, blood/hemoglobin, protein
- l For women of childbearing potential (WOCBP): Serum pregnancy test for screening (central laboratory); urine pregnancy test at site for subsequent monitoring

Note: Telephone counseling will be available at any time as require

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3 LIST OF ABBREVIATIONS

ADA:	American Diabetes Association
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BMI:	body mass index
CI:	confidence interval
DBP:	diastolic blood pressure
DTSQ:	diabetes treatment satisfaction questionnaire
ECG:	electrocardiogram
FPG:	fasting plasma glucose
FSH:	follicle stimulating hormone, serum follicle stimulating hormone
GLP-1:	glucagon like peptide-1
HbA1c:	glycated hemoglobin A1c
HLGT:	high-level group term
HLT:	high level term
IMP:	investigational medicinal products, investigational medicinal product
IRB/IEC:	Institutional Review Board/Independent Ethics Committee
ITT:	intent-to-treat
IVRS/IWRS:	interactive voice response system/interactive web response system
MedDRA:	Medical Dictionary for Regulatory Activities
MMRM:	mixed-effect model with repeated measures
NIMP:	non-investigational medicinal product
NYHA:	New York Heart Association
OADs:	oral antihyperglycemic drugs
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PK:	pharmacokinetic
PRO:	patient reported outcome
PT:	preferred term
PTC:	product technical complaint
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SC:	subcutaneous
SD:	standard deviation
SMPG:	self-monitored plasma glucose
SOC:	system organ class
SU:	sulphonylurea
T2DM:	type 2 diabetes mellitus

TEAE: treatment emergent adverse event
ULN: upper limit of normal

4 INTRODUCTION AND RATIONALE

The progressive nature of type 2 diabetes requires introducing insulin therapy to achieve appropriate glycemic control in many patients at certain stage of the disease. Clinicians face challenge when advising patients to start insulin despite clear evidence that good glycemic control reduce microvascular, and to a lesser degree, macro-vascular complication. The key barriers appear to be both patient and physician related factors: fear of pain and needles, concern of side effects of insulin (ie, hypoglycemia, weight gain etc) and the complexity of delivering the insulin despite marked improvement in the delivery process. The major facilitators of insulin initiation focus on clinical benefits of insulin in reducing symptoms and complications as well as improving survival and quality of life (1).

Basal insulin forms the cornerstone of many treatment regimens for type 2 diabetes. Basal insulin alone is recommended by American Diabetes Association (ADA) as the most convenient initial insulin regimen (2). Recently two new basal insulin preparations (Toujeo[®] and Tresiba[®]) have been introduced to clinical practice with the potential to address some of the concerns around initiating insulin therapy will facilitate patients and physicians to make decision on insulin initiation and keep better compliance and then contribute to long term glycemic control for patients. Comparison of these new basal insulins in insulin naive patients with type 2 diabetes inadequately controlled with OADs would provide meaningful information on their use for clinical practice.

Insulin glargine U100 (Lantus[®]) is 21A-Gly-30Ba-L-Arg-30Bb-L-Arg human insulin, a recombinant analog of human insulin providing a 24-hour basal insulin supply after a single-dose SC injection. Its efficacy and safety are well-known through extensive data collection involving over 200 000 patients in clinical studies and observational studies (3).

HOE901-U300 (Toujeo) has the same composition as the current Lantus formulation 100 U/mL with adjustment of 3-times the amount of active pharmaceutical ingredient and corresponding Zn content. The time-action profile of Toujeo was investigated in preclinical and clinical pharmacology studies and can be characterized as more even and prolonged profile of the glucose lowering activity (up to 36 hours) compared to insulin Lantus. Its efficacy and safety were demonstrated in the EDITION program. The glucose lowering effect of Toujeo was comparable with Lantus but lower hypoglycemia risk in type 2 diabetes mellitus (T2DM) population. EDITION 3 study which studied an insulin naive population demonstrated that in comparison with Lantus, hypoglycemia risk was reduced in nocturnal severe and/or confirmed hypoglycemia (plasma glucose <3.9 mmol/L) and severe and/or confirmed hypoglycemia <3.0 mmol/L in any time of the day. Toujeo has been approved in the US, the European Union, Japan, and other parts of the world. Further information on Toujeo, including important clinical trials performed pre- and post-registration, can be found in the national product label or in the Product Information (4) and Investigators Brochure HOE901 (3).

Tresiba 100 unit/mL solution for injection in pre-filled pen (insulin degludec) is a new recombinant analog of human insulin providing basal insulin supply beyond 42 hours after injection in euglycemic clamp conditions in type 1 diabetes (5). Its efficacy and safety were

demonstrated in BEGIN program. The impact of Tresiba on glycated hemoglobin A1c (HbA1c) was comparable with insulin Lantus but with reduced risk of hypoglycemia mainly during the protocol defined nocturnal period (6). In the BEGIN Once Long study which investigate the efficacy and safety with Tresiba versus Lantus in similar population as EDITION 3 (7), overall rates of confirmed hypoglycemia (plasma glucose <3.1 mmol/L or severe) were similar with Lantus. However lower nocturnal confirmed hypoglycemia was shown in favor of Tresiba (8). 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 Product label Information on FDA website (5).

Both Toujeo and Tresiba took Lantus as active comparator and demonstrated comparable efficacy and lower hypoglycemia risk in T2DM but no head-to-head comparison was performed. This trial is designed to confirm Toujeo's efficacy and safety in comparison with Tresiba in insulin-naïve patients with T2DM inadequately controlled with non-insulin anti-diabetic medication and requiring basal insulin initiation. It will test the hypothesis that glucose control with Toujeo is non-inferior to Tresiba. Based on the currently available medical evidence and the application of the treat-to-target concept, comparable efficacy is expected. HbA1c reflects the average glycemia over 2-3 months and has strong predictive value for diabetes complications. It is accepted by regulatory agencies, scientific association as an appropriate primary endpoint to support a claim based on glycemic control (9),(10).

In the EDITION trials Toujeo was associated with lower hypoglycemia risk than Lantus during the initial phase (first two months when most of the insulin titration occurred) and the hypoglycemia benefit was maintained until the end of the trials (6 months) in T2DM. Tresiba demonstrated comparable hypoglycemia risk to Lantus during the titration phases (0-15 weeks of treatment) and in favor of Tresiba with lower hypoglycemia risk beyond Week 16 in insulin naive population (6). Hence, the results from this head to head comparison of Toujeo with Tresiba in term of hypoglycemia will be of particular interest.

Secondary objectives are to assess the effects of Toujeo versus Tresiba on percentage of patients reached HbA1c target, including not only reaching the target but also without severe and/or confirmed hypoglycemia. The analysis of the effects of the flat insulin profile over at least 24 hours will be assessed based on self-monitored plasma glucose (SMPG) measurements (eg, 4-point, 8-point glucose profiles, fasting plasma glucose [FPG]). Safety evaluation will include the comparison of all hypoglycemia events occurrence frequency and distribution, local tolerability at injection site, hypersensitivity reactions and other treatment emergent adverse events (TEAEs). Repeat assessments of PRO will be performed during the study (Including patient satisfaction with treatment and patient perception of blood glucose control assessed by Diabetes Treatment Satisfaction Questionnaire (status and change version) (DTSQ and DTSQc) questionnaires (11),(12) and Hypoglycemia Attitudes and Behavior Scale (HABS) (13) with a particular focus on patient's attitudes and behavior related to hypoglycemia in T2DM. Nocturnal hypoglycemia timeframe is defined as during standardized period (0:00 to 5:59 AM) and extended period (0:00 to 7:59 AM) and at sleep status to observe the hypoglycemia event when patients are usually at sleeping period, usually in fasting condition. The extended period allow both Toujeo and Tresiba effect reaches a maximum (Toujeo: reach a stable plateau from 11 to 12 hours after dosing. Tresiba: a median of 12 hours post-dose) which anticipate more hypoglycemia episode in the early morning.

The target study population will comprise of adult T2DM patients who are naïve to insulin use, and considered to be inadequately controlled on their current antidiabetic medications (HbA1c between 7.5 and 10.5% and pre-study antidiabetic therapy have been stable for type and dose for at least 3 months before screening). It is expected that the investigator will exercise sound clinical judgment in assessing the patient's eligibility in meeting the study inclusion/exclusion criteria and the individual evaluation of the expected benefits of improved glycemic control versus treatment risks (eg, Hypoglycemia). The inclusion of insulin naïve patients will provide valuable information around insulin initiation and dose titration for both compounds in this population.

The starting dose of Toujeo and Tresiba was recommended as 0.2 U/Kg and 10 U once daily in accordance with product label and follow the same insulin titration algorithm. Injections of IMPs will be given during 6:00 PM to 8:00 PM to compare both IMP in comparable situation, such as avoid potential bias of timing of hypoglycemic events during the day (eg, nocturnal versus other) based on the different pharmacokinetic (PK) and pharmacodynamic (PD) profiles. Pen injectors will be used which should maximize convenience and minimize dosing errors. Background treatment should remain stable (type and dose) during the study, including SU and meglitinide, at least until basal insulin doses and HbA1c levels have stabilized, except for discontinuation of agents not approved in combination with insulin according to local labeling/local treatment guidelines before randomization and any identified safety concerns necessitating a reduction in dose or discontinuation of background non-insulin antidiabetic drug(s) during the trial, after randomization. Rescue therapy may be given for refractory hyperglycemia after Week 12. The choice of the anti-diabetic treatment to be added to the basal insulin should be based on Investigator's decision and local labeling documents, either adding an increase in dose of one of the background agents the patient was taking at randomization, or in the form of another oral agent or an injectable such as prandial insulin may be the preferred option or a glucagon like peptide-1 (GLP-1) receptor agonist.

A screening period of 2 weeks is designed to allow patients to familiarize themselves with the glucose meter, diary; and to be counseled in appropriate lifestyle practices as well as the symptom of hypoglycemia and hypoglycemia management. Only if any of the laboratory parameters are not available upon the end of the screening period (eg, sample material damaged during transport etc), a retest can be performed. If this is the case (and exceptionally in other situations if justified) the screening period can be extended of one additional week. Twelve (12) weeks are anticipated for study drug dose titration which should allow most patients have time to reach a stable dose, with another 12 weeks to allow HbA1c value to stabilize at this dose. A dose titration schedule will be recommended (dose increases for fasting SMPG values above target ranges of 80-100 mg/dL (4.4-5.6 mmol/L), and dose reductions for lower values or occurrence of symptomatic confirmed hypoglycemia). Weekly site contacts with the patient (at time of on-site visits or by phone) should occur during the titration period (through Visit 14) to titrate the dose of study drug based on review of the interval SMPG readings, any hypoglycemia events, and overall clinical situation. Because patients are beginning a new insulin treatment, participants in this trial will be encouraged to perform frequent SMPG monitoring, especially fasting values and any time if hypoglycemia occurred, in order to provide optimal data for study drug titration, and to confirm episodes of low blood glucose. Seven days post-treatment safety assessment is designed to be performed by phone to check for problems/AEs after completion of study treatment at the end of

the study or after premature discontinuation of study (except patient who prematurely discontinues the study treatment but continues in the study up to the scheduled date of study completion).

A sample size of 920 patients (460 with Toujeo and 460 with Tresiba) will ensure that the upper confidence limit of the two-sided 95% CI for the adjusted mean difference between Toujeo and Tresiba would not exceed 0.3% HbA1c with 90% power assuming that standard deviation (SD) is 1.4%, and that the true difference between Toujeo and Tresiba is zero in HbA1c. Patients will be stratified by their HbA1c (<8.0%; ≥8.0%) and SU or meglitinide using (Yes versus No) due to the concomitant of SU/meglitinide will increase the occurrence of hypoglycemia events overall.

This is a Phase 4 study. Benefit and risk of both investigational medical products had been demonstrated by clinical studies and approved by health authorities (4),(3),(5).

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to demonstrate the non-inferiority of Toujeo to Tresiba in HbA1c change from baseline to Week 24 in insulin naive patients with type 2 diabetes not adequately controlled with OADs with or without GLP-1 receptor agonist.

5.2 SECONDARY

The secondary objectives of this study are

- To assess the effects of the insulin Toujeo in comparison with insulin Tresiba on:
 - HbA1c change over 12 weeks
 - Fasting plasma glucose (FPG) change over 12 weeks and 24 weeks
 - Fasting Self-Monitored Plasma Glucose (SMPG) and 4-point SMPG and 8-point SMPG profile change over 12 weeks and 24 weeks
 - Mean 24-hour plasma glucose over Week 12 and Week 24
 - Variability of fasting SMPG and 24-hour plasma glucose over Week 12 and Week 24
 - Percentage of patients reaching HbA1c targets $<7\%$ or $\leq 6.5\%$ at Week 12 and Week 24
 - Percentage of patients reaching HbA1c targets $<7\%$ or $\leq 6.5\%$ at Week 12 and Week 24 without severe and/or confirmed hypoglycemia during the 12 weeks and 24 weeks treatment period
 - Percentage of patients requiring rescue therapy during the 24 weeks of treatment
- To assess the frequency of occurrence and diurnal distribution of hypoglycemia by category of hypoglycemia (symptomatic, asymptomatic, nocturnal, severe, probable and pseudo)
- To assess the safety in each treatment group over 24 weeks treatment
- To assess the treatment effects in each treatment group on Patient Reported Outcomes (PROs) measured by the following questionnaires:
 - Diabetes Treatment Satisfaction Questionnaire (DTSQ, status version and change version)
 - Hypoglycemia Attitude and Behavior Scale (HABS)

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a multicenter, open-label, 1:1 randomized, active-controlled, 2-arm, parallel-group, 24-week treatment duration Phase 4 study.

The study will recruit outpatients with T2DM inadequately controlled on OADs with/without GLP-1 receptor agonist. At the end of the screening period, eligible patients will be randomized to one of two treatment groups:

- Insulin Toujeo group
- Insulin Tresiba group

The randomization will be stratified by value of HbA_{1c} at the screening visit (<8%, ≥8%) and sulphonylurea (SU) or meglitinides use before the day of screening (Yes; No).

The study will comprise 3 periods:

- An up to 2-weeks screening period. It can be exceptionally extended up to one additional week
- A 24-week open-label randomized treatment period
- A 7-day post-treatment safety follow-up period for all the patients after permanent investigational medical product (IMP) discontinuation (except for patients who prematurely discontinue the study treatment but continue in the study)

The type and dose of antidiabetic background therapy will remain unchanged during the study (see [Section 8.3.1](#)).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The maximum study duration per patient will be approximately 27 weeks: an up to 2-week screening period, a 24-week randomized treatment period, and a 7-day post-treatment safety follow-up period.

6.2.2 Determination of end of clinical trial (all patients)

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

6.3 INTERIM ANALYSIS

No interim analysis is planned.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

- I 01. Adult patients with T2DM inadequately controlled with OADs therapy with/without GLP-1 receptor agonist at stable dose for at least 3 months
- I 02. Signed written informed consent

7.2 EXCLUSION CRITERIA

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

7.2.1 Exclusion criteria related to study methodology

- E 01. HbA1c <7.5% or >10.5% (at screening)
- E 02. History of T2DM for less than 1 year before screening
- E 03. Less than 6 months before screening on OAD(s) treatment and GLP-1 receptor agonist (if taken);
- E 04. Current or previous insulin use except for a maximum of 8 consecutive days or totally 15 days (eg, acute illness, surgery) during the last year prior to screening;
- E 05. Initiation of new glucose-lowering medications and/or weight loss drug in the last 3 months before screening visit;
- E 06. Patient receiving only non-insulin antidiabetic drugs not approved for combination with insulin according to local labelling/local treatment guideline
- E 07. Age <18 years at time of informed consent
- E 08. Body Mass Index (BMI) <25 kg/m² or >40 kg/m²
- E 09. History of hypoglycemia unawareness or repeated episodes of severe hypoglycemia or metabolic acidosis, including hospitalization for diabetic ketoacidosis during the last 12 months prior to screening;
- E 10. Use of an investigational drug within 1 month or 5 half-lives, whichever is longer, before screening
- E 11. Uncontrolled treated/untreated severe hypertension (systolic blood pressure [SBP] >180 mmHg and/or diastolic blood pressure [DBP] >95 mmHg) at screening

- E 12. History of myocardial infarction, stroke, or heart failure requiring hospitalization within the last 3 months prior to screening
- E 13. Unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema likely to require treatment (eg, laser, surgical treatment or injectable drugs) during the study period;
- E 14. History of drug or alcohol abuse within 6 months prior to screening
- E 15. Conditions/situations such as:
- Patients with conditions/concomitant diseases making them non-evaluable for primary efficacy endpoint(eg, hemoglobinopathy or hemolytic anemia, receipt of blood or plasma products within 3 months prior to screening visit or plan to receive transfusion of blood or plasma products during the screening period)
 - Patients with severe or unstable hepatic, gastrointestinal, cardiovascular (including congestive heart failure NYHA III/IV), respiratory, neurological, psychiatric, hematological, renal, endocrine, dermatological disease, active malignant tumor, other major systemic disease or patients with short life expectancy or any other medical condition that might interfere with the evaluation of study medication according to investigator's medical judgment
 - Patients potentially at risk of noncompliance to the study procedure (eg, mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, including blood glucose monitoring requirements, the documentation of SMPG data and insulin dosing, evidence of an uncooperative attitude and/or inability to return for follow-up visits, and unlikely to complete the study)
 - Patient is the Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol
- E 16. Use of systemic glucocorticoids (excluding topical application or inhaled forms) for one week or more within 3 months prior to the time of screening
- E 17. End-stage renal disease defined as estimated GFR (MDRD) $<15 \text{ mL/min/1.73 m}^2$ (14) or being on hemodialysis
- E 18. Active liver disease or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times upper limit of normal (ULN) or total bilirubin >1.5 times ULN (except in case of documented Gilbert's syndrome) at screening
- E 19. Nightshift workers
- E 20. Likelihood of requiring non-permitted medications during the treatment period
- E 21. Pregnant or breast-feeding women

- E 22. Women of childbearing potential with no effective contraceptive method of birth control and/or who are unwilling or unable to be tested for pregnancy or women who intend to become pregnant during the study period (see [Appendix D](#) for country specific requirement)

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

- E 23. Any contraindication to Tresiba according to the National Product labeling; history of hypersensitivity to the active substance or to any of the excipients of Tresiba
- E 24. Any contraindication to the background non-insulin antidiabetic medication according to the respective National Product labeling

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

- E 25. Any contraindication to Toujeo according to the National Product labeling; History of hypersensitivity to the active substance or to any of the excipients of Toujeo

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

- E 26. Patient who has withdrawn consent before randomization
- E 27. Despite screening of the patient, randomization is stopped at the study level

Note: A patient should not be randomized more than once. Patients can be re-screened once before randomization in case of non-evaluable exclusion criteria or in cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment.

8 STUDY TREATMENTS

8.1 DIET AND EXERCISE

Lifestyle and diet counseling provided before the time of screening is to be continued during the study.

Compliance with the diet and lifestyle recommendations will be discussed with the patient throughout the study, and more specifically in case of insufficient glucose control (please refer to [Section 8.3.2](#)).

8.2 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Insulin Toujeo (Insulin glargine 300 U/mL) and insulin Tresiba (Insulin Degludec 100 U/mL) are considered as investigational medicinal products (IMPs).

8.2.1 Formulations

Toujeo (Insulin glargine 300 U/mL)

Toujeo (Insulin glargine 300 U/mL) is supplied as a sterile, non-pyrogenic, clear, colourless 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 units/mL insulin glargine solution).

Mixing of Toujeo with other insulin products or dilution is not allowed.

Tresiba[®] (Insulin Degludec 100 U/mL)

Tresiba (Insulin Degludec 100 U/mL) is supplied as a sterile, non-pyrogenic, clear, colourless solution for SC injection in the marketed Tresiba[®] FlexTouch prefilled, disposable pen. Each Tresiba FlexTouch contains in total 300 units of insulin degludec (3 mL of 100 units/mL insulin degludec solution).

Mixing of Tresiba with other insulin products or dilution is not allowed.

8.2.2 Injection devices and training to use injection devices

8.2.2.1 Injection devices

Toujeo (Insulin glargine 300U/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.

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

Insulin 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:

- NovoFine needles
- NovoTwist needles

Or

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

8.2.2.2 Training to use injection devices

An instruction leaflet will be provided which explains how to use the disposable pen and needles. All patients will be trained by study staff at Visit 2 (randomization) on how to use the pen correctly, how to store it and how to change the needle and ensure patient has the competence of self-injection (eg, set correct dose; change the needles; identify the correct injection area; complete the injection; know the appropriate storage conditions; conduct simple troubleshooting etc). The patient's family member or usual caregiver, if applicable, is highly encouraged to attend training with the patients as he/she plays a key role and is able to support the patient with study related procedures during the study. Training will be repeated as often as deemed necessary by study site staff during the treatment period. For the duration of the treatment, the patients will be required to use the same type of study drug disposable pens and needles. The pen and leaflet that patient will need to use during the treatment period will be dispensed according to the visit. Each patient is supplied with the appropriate number of pens according to the dispensing scheme indicated in the study flowchart (see [Section 1.2](#)).

Pen-device issues (malfunctions) must be reported to the sponsor via the procedure for product technical complaint (PTC), using the respective PTC form, which is described in a separate manual.

Injection pens should never be shared with others, even if the needle is changed. Patients must 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.

8.2.3 Dosage schedule

Injection time

Toujeo and Tresiba will be self-administered by SC injections once daily between 6:00 PM and 8:00 PM throughout the study period. The injection time will be selected at the discretion of patients and investigators at V2.

Injection site

The IMP should be self-administered by deep SC injection, alternating between the left and right anterolateral and left and right posterolateral abdominal wall or thighs or upper arms. Within a given area, location should be changed (rotated) at each time to prevent injection site skin reactions.

The injection sites for IMP and non-investigational medicinal product ([NIMP], if taken) should be different so that, if any, an injection site reactions can be attributed specifically either to IMP (Toujeo or Tresiba) or NIMP (eg, GLP-1 receptor agonist).

8.2.4 Starting dose and dose adjustments

Starting dose

The recommended daily starting dose of each IMP is defined per label with once daily as below followed by individual dose adjustment:

- Toujeo: 0.2 units/kg (4)
- Tresiba: 10 units (5)

Dose adjustment

During the study, doses of either basal insulin, Toujeo or Tresiba will be titrated to achieve glycemic targets without hypoglycemia according to the same algorithm as below ([Table 2](#)).

- After randomization, 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 80 to 100 mg/dL (4.4 to 5.6 mmol/L) while avoiding hypoglycemia episodes.
- Thereafter, until the end of the study, the dose will be adjusted as necessary to maintain this fasting SMPG target.
- Dose adjustments are based on a median of fasting SMPG values from the last 3 measurements, which include the value measured on the day of titration, measured by the patient using glucometers and accessories supplied by the sponsor.

The best efforts should be made to reach the target glucose by 8-12 weeks after randomization.

Table 2 - Dose adjustment algorithm

Median ^a of fasting SMPG (mg/dL) from the last 3 measurements	Toujeo® and Tresiba® dose change ^b
>140 (7.8 mmol/L)	+ 6 U
>120 and ≤140 (>6.7 and ≤7.8 mmol/L)	+ 4 U
>100 and ≤120 (>5.6 and ≤6.7 mmol/L)	+ 2 U
≥80 and ≤100 (>4.4 and ≤5.6 mmol/L)	No change
<80 (<4.4 mmol/L) or occurrence of 1 symptomatic confirmed hypoglycemia episode documented in the preceding week	-2U or at the discretion of the investigator

^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 Dose adjustment should not be more often than every 3 days.

Sound clinical judgment is to be exercised while titrate patients. Investigators may adjust or stop titration, or temporarily reduce dose if they believe further titration would be hazardous at that time.

Patients will be educated about the titration schedule so that they can monitor it with the assistance of the investigator or medically qualified designee. All discussions must be properly documented in the patient's record. 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 IMP insulin dose adjustments in between scheduled visits without prior consultation of the site personnel.

Data relevant for IMP titration (eg, fasting SMPG, daily insulin dose, hypoglycemia occurrence) will be reviewed by dedicated independent persons regularly to identify patients whose basal insulin dose was not titrated according to the recommended dose adjustment algorithm. If needed, re-training of site staff (including investigator) on titration will be performed. The details on insulin titration monitoring will be provided in separate documents.

8.3 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Background OADs and GLP-1 receptor agonist (if taken) and rescue medication will be considered as NIMP(s).

8.3.1 Anti-diabetic background therapy

The type and dose of anti-diabetic background therapy will remain unchanged during the study unless agents not approved in combination with insulin according to local labeling/local treatment guideline (if used, they will be discontinued at the start of the IMP) or identified safety concerns necessitate a reduction in dose or discontinuation of non-insulin antidiabetic drug(s).

Anti-diabetic background treatment dose and type is to be reported in the e-CRF.

8.3.2 Rescue therapy:

Routine fasting SMPG, central laboratory FPG measurements and central laboratory alerts on HbA1c are set up to ensure that glycemic parameters remain under predefined threshold values. The threshold values for rescue are defined as follows:

From visit 14 (Week 12): FPG >200 mg/dL (11 mmol/L) and / or HbA1c >8.5%.

In case of FPG or HbA1c above the thresholds, 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 (ie, After at least 8 hours fasting)
- **Study treatment is being properly titrated according to the protocol,**
- There is no intercurrent disease which may jeopardize glycemic control (eg, infection),
- Compliance to treatment, diet and lifestyle is appropriate.

If any of the above can reasonably explain the insufficient glycemic control, the investigator should undertake appropriate action, ie:

- Titrate basal insulin dose according to the protocol,
- Initiate an evaluation and treatment of any intercurrent disease (to be reported in AE/SAE/concomitant medication parts of the e-CRF and the medical record),
- Stress the absolute need to comply with treatment, diet and lifestyle recommendations,
- Schedule an HbA1c and/or FPG assessment at the next visit (if the next visit is a phone call, it should be replaced by an on-site visit).

If none of the above reasons can be found, and/or appropriate actions fail, it is recommended to initiate rescue therapy. The choice of the anti-diabetic treatment to be added to the basal insulin should be based on Investigator's decision and local labeling documents. Adding prandial insulin may be the preferred option. The addition of a new antidiabetic drug or increase in dose of background antidiabetic medication ("rescue") should not be decided based on a single FPG or HbA1c value but be based on a thorough evaluation of the patient's glycemic control.

The reason for initiating rescue therapy, type of rescue therapy and the day of starting rescue therapy along with the dose will be documented on the appropriate pages of e-CRF.

Note: Short-term (up to 10 days maximum) uses of short/rapid-acting insulin therapy (eg, due to acute illness or surgery) will not be considered as rescue therapy. All such use of short/rapid-acting insulin therapy must be reported in the e-CRF and patient record.

All assessments for primary and secondary efficacy and safety parameters planned in final on treatment assessment visit (Visit 20) should be performed before adding the "rescue medication". Then the patient continues the IMP and stays in the study in order to collect safety information.

8.4 BLINDING PROCEDURES

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

COMPENSATION FOR LACK OF BLINDING

Despite the open-label administration of IMP, assessment of outcomes will be based on objectively collected data, which are assessments for the efficacy variable (HbA_{1c}, FPG) by central laboratory blinded to study treatment groups.

As Toujeo and the control drug Tresiba are distinguishable in terms of initial dose and following doses during the first weeks of the study, a process will be applied to blind this information at the sponsor study team level.

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 and dose of IMP throughout the study up to the database lock. All analyses and data review before database lock will be performed blindly, except for the titration review which will be performed by an independent reviewer.

Insulin titration review will be performed by reviewing the data related to fasting SMPG, hypoglycemia events and IMP dose titration by independent reviewer.

The first Statistical Analysis Plan (SAP) will be written before the first patient is randomized in the study.

8.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The Trial Supply Operations Manager provides the treatment kit number list and the Study Biostatistician provides the randomization scheme to the interactive voice response system (IVRS)/interactive web response system (IWRS). Then, the IVRS/IWRS generates the patient randomization list according to which it allocates treatment arms to the patients.

The study medications are provided in open-label boxes and each type of kit is identified with a treatment number.

At the screening visit the investigator or designee contacts the IVRS/IWRS center to receive the patient number. The patient number is composed of 9-digit number containing the 3-digit country code, the 3-digit center code and the 3-digit patient chronological number (which is 001 for the first patient screened in a center, 002 for the second patient screened in the same center etc).

Patients are randomized to receive during the 24 weeks comparative efficacy and safety period, either Toujeo or Tresiba. The randomization ratio is 1:1. The randomization is stratified by screening HbA_{1c} value (<8%, ≥8%) and SU or meglitinides use before the day of screening (Yes; No).

The treatment kits are allocated using a centralized treatment allocation system (IVRS/IWRS). On V2 (D1), after assessment results are reviewed and baseline assessment is completed, IVRS/IWRS is contacted for randomization and the first treatment kit(s) allocation. The investigator or designee has to call the IVRS/IWRS to provide some information (such as patient number provided by IVRS/IWRS at screening visit, date of birth, etc). Afterwards the IVRS/IWRS is contacted again each time a new treatment kit(s) allocation is necessary, ie, at Weeks 4, 8, 12, 16 and 20. The IVRS/IWRS will allocate treatment kit(s) using their treatment number.

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

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

8.6 PACKAGING AND LABELING

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

The appropriate number of kits will be dispensed to cover up to the next dispensing visit (please refer to the study flowchart in [Section 1.2](#)).

Toujeo SoloStar disposable pre-filled pen containing a 1.5 mL solution of insulin glargine 300 U/mL will be supplied as open label treatment kits containing 5 Toujeo SoloStar pens.

Tresiba FlexTouch disposable pre-filled pen containing 3 mL solution of insulin degludec 100 U/mL will be supplied as open label treatment kits containing 5 Tresiba FlexTouch pens.

Treatment labels will indicate the treatment number used for treatment allocation. The Investigator's name, the patient number, visit number and box number will be entered manually by the site staff on the treatment box label prior to dispensing.

8.7 STORAGE CONDITIONS AND SHELF LIFE

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

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

The expiry date is mentioned on the IMPs labels, and storage conditions are written on the IMPs labels and in the instruction leaflet. Patients are responsible for the correct storage of "unused" and "in-use" pens after it is dispensed at the site.

8.8 RESPONSIBILITIES

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

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

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure. Pen-related deficiencies should be reported to the sponsor by the means of a procedure on product technical complain (PTC) form (please see [Section 8.2.2.2](#)).

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

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

8.8.1 Treatment accountability and compliance

A Treatment Log for returned and dispensed IMP will be kept for each patient. At each on-site visit, patient returns to the site with used and unused IMP except for Visit 4 (collecting used study medication only). Investigator or delegate has to inspect IMP remaining in the returned packs and compare to dosing records documented in the patients' diaries. Discrepancies have to be addressed to the patient for clarification of real treatment administration. The investigator completes the appropriate treatment log based on the used/unused IMP (study drug pens) returned.

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

Patients have to record the administration of their background non-insulin antidiabetic medication(s) and rescue therapy (if applicable) in the diary. The following information with regards to the NIMP will be recorded in the source data: drug(s) name, dosage, start date, stop date. Compliance will be checked by interviewing the patient at each visit and be documented in the source documents.

8.8.2 Return and/or destruction of treatments

IMP

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.

NIMP

As NIMP is not provided by the study sponsor, return and destruction isn't required.

8.9 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). Treatments in addition to the study treatment should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the investigator, with a stable dose (when possible). Any treatment which are continued during the study and/or initiated or changed during the study must be recorded in source data and in the e-CRF.

Prohibited concomitant therapy

The following drugs are not permitted during the screening and randomized open-label treatment periods:

- Antidiabetic drugs, which are not approved in combination with insulin according to local labeling/local treatment guideline, are prohibited throughout the on treatment period of the study,
- No other additional antidiabetic treatments (eg, meal time insulin), apart from authorized concomitant non-insulin antidiabetic therapy and, when applicable rescue therapy (see [Section 8.3.2](#)), are to be used until the end of the study,
- **Note:** Short-term use (≤ 10 days) of rapid/short-acting insulin due to acute illness or surgery (eg, infection) is allowed,
- Insulin pump therapy is not allowed during the course of the study,
- Initiation of weight loss drugs during the study is not allowed. Previous treatment with weight loss drugs can be continued but the doses must have been stable for at least 3 months prior to screening and must remain stable throughout the study,

- Use of systemic glucocorticoids for more than 10 days (topical or inhaled applications are allowed) is prohibited,
- Other medications are allowed as needed; however doses of chronically administered medicines should be kept fixed during the trial if at all possible.

Note: After permanent IMP discontinuation (per protocol or premature) any treatments are permitted, as deemed necessary by the Investigator.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

In case of using rescue therapy, all assessments planned for the Visit 20 (Week 24) are to be performed before initiating rescue therapy. After these assessments are completed and rescue therapy has been initiated, the patient will remain in the study and continue with their study treatment as well as background non-insulin anti-diabetic drugs if appropriate. The planned visits and assessments should be performed until the last scheduled visit.

In case of premature and permanent IMP discontinuation, patients should have a visit as soon as possible with the assessments normally planned in Visit 20 (Week 24). Afterward, the patients should continue in the study up to the scheduled date of study completion. They should be followed up according to the study procedures as specified in the protocol (except for the 7-day safety post-treatment follow-up).

Data quality being very important to fully evaluate the efficacy/safety of the IMP, investigators must make their best efforts educating their patients on the importance of sticking to visit schedules, study required procedures and assessments up to the end of the study. A particular effort is requested to prevent missing data.

9.1 PRIMARY ENDPOINT

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

9.1.1 Primary endpoint

- Change in HbA1c from baseline to Week 24.

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I “National Glycohemoglobin Standardization Program” (NGSP) central laboratory.

HbA1c is assayed at screening (Visit 1, Week -2); at baseline (Visit 2; Day 1); at Visit 10 (Week 8); Visit 14 (Week 12); and Visit 20 (Week 24; final primary endpoint assessment visit).

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoint(s)

- Change in HbA1c from baseline to Week 12,
- Change in FPG from baseline to Week 12 and Week 24,
- Change in fasting SMPG from baseline to Week 12 and Week 24,
- Change in 4-point SMPG and 8-point SMPG profiles per time-point from baseline to Week 12 and Week 24,

- Change of mean 24-hour plasma glucose based on 8-point SMPG from baseline to Week 12 and Week 24,
- Change in variability of fasting SMPG and 24-hour plasma glucose based on 8-point SMPG from baseline to Week 12 and Week 24,
- Percentage (%) of patients reaching target HbA1c <7% and ≤6.5% at Week 12 and Week 24,
- Percentage (%) of patients reaching target HbA1c <7% and ≤6.5% at Week 12 and Week 24 without severe and/or confirmed hypoglycemia (70 mg/dL and 54 mg/dL as cut off point) during the 12 weeks and 24 weeks treatment period,
- Percentage (%) of patients with SU or meglitinide dose reduction/discontinuation due to hypoglycemia over 24 weeks of treatment,
- Percentage of patients requiring rescue therapy during 24 weeks treatment period,
- Basal insulin dose (U and U/kg body weight): change from baseline to Week 12 and Week 24.

Observation period of efficacy endpoints

The 24-week on-treatment period for efficacy endpoints (primary and secondary efficacy endpoints) is defined as the time from the first injection of open-label IMP up to 7 days after date of last IMP administration for HbA1c, 0 day for 4-point and 8-point SMPG and insulin dose, 1 day for FPG and fasting SMPG, 2 days for hypoglycemia after the last injection of open-label IMP or up to the introduction of rescue therapy, whichever is the earliest.

The randomized 24-week period for efficacy variables is defined from first dose of IMP up to Week 24, regardless of study treatment discontinuation and intake of rescue therapy.

The baseline value for efficacy endpoints is the last available value prior to the first injection of open-label IMP.

9.2.1.1 Fasting plasma glucose

Fasting plasma glucose is measured at a central laboratory.

Blood samples for FPG measurement are taken at baseline (Visit 2; Day 1); at Visit 10 (Week 8); Visit 14 (Week 12); and Visit 20 (Week 24; final primary endpoint assessment visit).

9.2.1.2 Self-measured plasma glucose (SMPG) and glucometer, patient diaries and training

9.2.1.2.1 Glucometer, patient diary and training

All the patients are supplied with a glucometer, the corresponding supplies (lancets, test strips, etc), a leaflet, and with diaries at the screening visit V1 (Week -2) in order to perform self-

measurement of plasma glucose, reporting information related to hypoglycemic event and record IMP doses etc. The patients will be instructed in the proper use of the glucometer and diary including education about hypoglycemia symptoms and management (See [Section 10.1.1.1](#)) at Visit 1 and repeated at Visit 2 to make sure good compliance to the instruction. The training will be repeated as often as necessary at the study visits. The patients will be instructed to bring their glucometers and patient diaries with them to each site visit. The glucometers should be calibrated according to instructions given in the package leaflet and the study site should also check the glucometers regularly using the provided control solutions for data validity.

Instruction on how to complete the patient diary on a daily basis will be done by site staff. At each on site visit:

- The study site staff reviews the patient's diary,
- SMPG values stored in the glucometer memory will be downloaded, printed out, dated, signed and filed into the patient file. If the patient has more than one SMPG reading at the same time point, the Investigator/site staff should discuss with the patient to identify the appropriate value to be recorded in the patient diary and in the e-CRF. This information will help the Investigator to assess treatment effects, adjust insulin doses and compliance.

Note: The SMPG values to be entered in the e-CRF must be checked for consistency with the information from the glucometer. In case of inconsistency, the reason for inconsistency has to be documented. If needed, the resulting action (eg, training of the patient on correct documentation of the values) is also to be documented. The confirmed values will be entered in the e-CRF based on the glucometer output values.

The **patient diary** includes but is not limited to the following information:

- Time and dose of daily IMP injections and type and dose of daily non-insulin antidiabetic medication(s),
 - In case of missed IMP injection, "0 unit" should be reported during the period when the IMP was not taken,
- Times of start of meals (breakfast, lunch and dinner) and SMPG measurements, as well as plasma glucose values at the day of the 4-point and 8-point SMPG test (see [Section 1.2](#)).
- Changes in anti-diabetic medication treatment,
- Adverse events, signs and symptoms suggesting occurrence of hypoglycemia and relevant onset time, countermeasure or corrective treatment, supportive test (ie, SMPG value) and outcome etc.

9.2.1.2.2 SMPG measurement

SMPG measurements include the following:

Fasting SMPG

Fasting SMPG will be used by the investigator and patients if appropriate to titrate and adjust insulin dose and to monitor glycemic control ([Section 8.2.4](#)). The fasting SMPG should be measured by the patient before breakfast and before the administration of the glucose-lowering agents once a day during the study. When up-titration has been completed and fasting SMPG is stable in the target range, at least 3 days measurements per week should be performed.

Fasting SMPG values should be recorded in the patient diary. The following daily fasting SMPG values will be entered in the e-CRF:

- All available fasting SMPG values from the week prior to each site or phone call visit and/or prior to insulin dose titration; these include the fasting SMPG value on the day of titration.

4-point (prebreakfast, prelunch, predinner, bedtime) SMPG Profile:

4-point SMPG profiles should be measured at the following 4 points: prebreakfast, prelunch, predinner and bedtime.

The patients are requested to perform 4-point SMPG profile measurement over a single 24-hour period on at least one day in the 5 days before V6 (Week 4) and V10 (Week 8). All SMPG values measured on these days will be recorded in the patient's diary and entered in the e-CRF (see [Section 9.2.1.2.1](#) and [Section 1.2](#)).

On the days when 4-point profiles are done, fasting SMPG will be considered as the first point of measurement, ie, "prebreakfast" time point.

8-point SMPG Profile:

The 8-point SMPG profile should be measured at the following 8 points: the 3:00 AM (+/-1 hour) at night, pre-prandial and 2 hours postprandial for breakfast, lunch, dinner and at bedtime. Two hours postprandial (breakfast, lunch and dinner) is defined as 2 hours after the start of the meal.

The patients are requested to perform 8-point SMPG profile measurement over a single 24-hour period on at least one day in the 5 days before **baseline visit (V2)**, V14 (Week 12) and V20 (Week 24, end of treatment assessment visit). Special attention should be paid that the 3:00 AM. All SMPG values measured on these days will be recorded in the patient's diary and entered in the e-CRF (see [Section 9.2.1.2.1](#) and [Section 1.2](#)).

On the days when 8-point profile are done, 4-point (prebreakfast, prelunch, predinner and bedtime) will be used for 4-point SMPG profile analysis.

SMPG during episodes of symptomatic hypoglycemia:

Whenever the patient feels hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible. Patients should be instructed to measure plasma glucose levels prior to the administration of glucose or carbohydrate intake whenever symptomatic hypoglycemia is suspected ([Section 10.6.1](#)), unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation.

The SMPG values and time of SMPG measurement, relevant countermeasures, symptom of hypoglycemia, assistance required or not, will be recorded in the patient diary and e-CRF.

Further SMPG:

The investigator may decide to request more frequent self-monitoring of plasma glucose if he/she considers necessary for the patient.

9.2.1.3 Dose of IMP

The patients document daily their IMP dose and time or any missed IMP injection in the patient diary.

The following values will be entered in the e-CRF:

- For the first 12 weeks (prior to V14, Week 12) of randomized treatment period:
 - Initial IMP starting dose of IMP
 - All available data on the injection time and doses administered will be entered in the e-CRF, including missed IMP injection
- After the first 12 weeks until the end of the randomized treatment period:
 - Daily dose and time of injection from the week last 3 days prior to each site or phone visit
 - In the case of any change in doses administered, the dose and injection time should be entered in the e-CRF
 - Missed IMP injection
- In case of symptomatic hypoglycemia (if appropriate), the dose and injection time should be entered in the e-CRF
- All available data of IMP dose and injection time on the last 3 days before permanently IMP treatment discontinuation

9.2.1.4 SU or meglitinide dose reduction/discontinuation due to hypoglycemia

The type and dose of antidiabetic background therapy will remain unchanged during the study but may have identified safety concerns necessitating a reduction in dose or discontinuation. The changes in antidiabetic medication administration and its reason should be documented in source data. If the dose reduction/discontinuation is due to hypoglycemia, the reason should be documented in e-CRF and report hypoglycemia event, eg, SU and meglitinide dose reduction due to hypoglycemia.

9.2.2 Safety endpoints

The safety endpoints are assessed by:

- Hypoglycemia events

Hypoglycemia will be classified as below category and analyzed using the following variables:

- Percentage of patients with at least one episode of confirmed hypoglycemia* and event rate during 24 weeks treatment periods,
 - Rate of hypoglycemia per month computed as: $365.25/12 \times (\text{number of episodes of hypoglycemia})/(\text{number of days exposed in time window})$,
 - Percentage of patients and event rate of hypoglycemia by study period (for ≤ 12 weeks, for >12 weeks to ≤ 24 weeks) to evaluate the potentially increased risk of hypoglycemia during the initial 12-week after starting treatment with basal insulin,
 - The diurnal distribution of the occurrence of each episode of confirmed hypoglycemia by category will be presented by two-hour timeframe over 24 hours during the 24 weeks treatment period.
- * Note: Confirmed hypoglycemia: Any hypoglycemia confirmed by plasma glucose below the cut off value (70 or 54 mg/dL). The cut-off value of 70 mg/dL (3.9 mmol/L) for defining hypoglycemia is in line with ADA hypoglycemia definition. The cut-off value of 54 mg/dL (3 mmol/L) is chosen because it represented a degree of hypoglycemia at which patients have typically neuroglycopenic symptom.
- Adverse events (AE) or serious adverse events (SAE) , including local tolerability at injection site, hypersensitivity reactions, Adverse events with special interest (AESI),
 - Vital signs,
 - Body weight.

Observation period of safety endpoints

The observation period of safety data will be divided into 3 segments:

- The **pre-treatment period** is defined as the time between the date of the informed consent and the first injection of open-label IMP
- The **on-treatment period** is defined as the time from the first injection of open-label IMP up to 7 days after the last injection of open-label IMP, regardless of the introduction of rescue therapy. The 7-day interval is chosen based on the half-life of the IMP (approximately 5 times the half-life of Tresiba)
- The **post-treatment period** is defined as the time starting 8 days after the last injection of open-label IMP (after on-treatment period)

The baseline value for safety endpoints will be the last available value prior to the first injection of open-label IMP.

9.2.2.1 Adverse events

Refer to [Section 10.4](#) to [Section 10.7](#) for details.

9.2.2.2 Hypoglycemia

Hypoglycemia will be assessed. Refer to [Section 10.6.1](#) for details.

9.2.2.3 Body weight

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer.

The use of balance scales is recommended; if digital scales are used, testing with standard weights is of particular importance. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The scale should be balanced with both weights at zero and the balance bar aligned. The patient should stand in the center of the platform as standing off-center may affect measurement. The weights are moved until the beam balances (the arrows are aligned). The weight is read and recorded in the e-CRF and Source Data. Self-reported weights are not acceptable; patients must not read the scales themselves. The body weight is measured at each on-site visit.

9.2.2.4 Laboratory safety variables

The clinical laboratory data consist of blood analysis, including hematology, clinical chemistry, serum pregnancy test in females of childbearing potential and serum follicle stimulating hormone (FSH) and estradiol (only in females requiring confirmation of postmenopausal status) and urinalysis. Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

Central laboratory data will be collected only at screening visit (Visit 1, Week -2) for identifying patients with exclusion criteria or safety consideration include serum pregnancy test will be test at screening visit. Urine pregnancy test at site will be performed at Visit 2 and end of treatment visit.

9.2.2.5 Physical examination

Physical examination is performed at screening visit (V1, Week-2), baseline visit (V2, Day 1) and end of treatment visit (V20, Week 24). Height is measured at V1 (see [Section 1.2](#)).

9.2.2.6 Vital signs

Vital signs include: systolic and diastolic blood pressure (mmHg) and heart rate (beat per minute: bpm). They are assessed at screening (Visit 1, Week -2); at baseline (Visit 2, Day 1), and all on-site visit (see [Section 1.2](#)).

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 (after the patient has rested comfortably for at least five minutes) and the values are

to be recorded in the e-CRF. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be recorded. Devices for blood 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.

Determination of the arm for blood pressure measurements:

At Visit 1 of the screening period, blood pressure has to be measured on both of the arms after 5 minutes in seated position and then again after two minutes in both arms in seated position. The arm with the higher diastolic pressure will be determined at this visit, identifying the reference arm for future measurements throughout the study. The highest value will be recorded in the e- CRF (all blood pressure values are to be recorded in the source data).

9.3 OTHER ENDPOINTS

9.3.1 Patient Reported Outcomes (Health-related Quality of Life)

The patient reported outcomes (PROs) measures in this study are the Treatment Satisfaction Questionnaire (DTSQs and DTSQc versions) and the Hypoglycemia Attitudes and Behavior Scale (HABS). They will be administered at Week 0 (Day 1, except for DTSQc), at Week 12 and at the end of the treatment. The questionnaires are attached in the Appendices (see [Appendix A](#), [Appendix B](#), [Appendix C](#))

The patients will be requested to complete the questionnaires by themselves during selected clinical visits (see study flow chart) in specific booklets, 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 to the investigator or his/her designee on the same day.

In case of rescue therapy: Administration of the three questionnaires (DTSQs, DTSQc and HABS) prior to the administration of the rescue therapy and afterwards as normally planned.

In case of early IMP discontinuation: Administration of the questionnaires at the visit planned for the last dosing day with IMP and afterwards as normally planned.

The Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs) is a validated questionnaire to assess patient satisfaction with treatment and patient perception of blood glucose control (11). It consists of 8 items that are answered on a Likert scale from 0 to 6. Items 1, 4, 5, 6, 7 and 8 are 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). DTSQs will be administered at baseline, 12 and 24 weeks in the local language.

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 (12). The change version has the same 8 items as the status version, with a small alteration to the wording of Item 7. 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. Items are answered on a Likert scale from -3 to +3, and the sum of the treatment satisfaction scores range from -18 to +18. Positive scores are indicative of improvement in treatment satisfaction, whereas negative scores are indicative of deterioration in treatment satisfaction. A score of 0 represents no change. The 2 items of 'perceived frequency of hyperglycemia' (Item 2) and 'perceived frequency of hypoglycemia' (Item 3) are scored from -3 ('much less of the time now') to +3 ('much more of the time now'), meaning negative scores indicate fewer problems with blood glucose levels and positive scores indicate more problems than before. DTSQc will be administered at 12 and 24 weeks in the local language.

At 12 and 24 weeks, DTSQs (status) will be administered before the DTSQc (change).

The **HABS (Hypoglycemia Attitudes and Behavior Scale)** was recently developed with type 2 diabetic patients using or not insulin (13). It consists of 14 items within 3 domains measuring anxiety (5 items), confidence (5 items) and avoidance (4 items) related to hypoglycemia. Items are answered on a Likert scale from 1 (strongly disagree) to 5 (strongly agree), with higher scores indicating high avoidance, confidence and anxiety related to hypoglycemia. The questionnaire will be administered at baseline, 12 and 24 weeks in the local language.

9.4 FUTURE USE OF SAMPLES

Not applicable

9.5 APPROPRIATENESS OF MEASUREMENTS

The primary efficacy endpoint of this study is change of HbA1c from baseline to endpoint (scheduled Week 24). HbA1c reflects the average glycemia over 2-3 months and has strong predictive value for diabetes complications. It is accepted by regulatory agencies and scientific association as an appropriate primary endpoint to support a claim based on glycemic control. Twenty-four weeks duration of study treatment is considered to be sufficient for achieving steady state conditions with Toujeo or Tresiba enabling an adequate assessment of time-dependent changes in HbA1c and the concomitant risk of hypoglycemia.

Most international consensus statements for standards of medical care in diabetes recommend to decrease HbA1c <7% to minimize the risk of developing complications. An even tighter threshold of HbA1c ≤6.5% is recommended in some guidelines (15). T2DM patients with HbA1c values in the target range and experiencing no hypoglycemia episodes are considered optimally managed for the disease. Secondary objectives are to analyze responder which is intended to justify clinical relevance of the observed reduction in HbA1c values. Therefore, analysis of responders is set up to compare both formulations in terms of rate of patients achieving and/or maintaining optimal long-term glycemia control confirmed by target HbA1c <7% or ≤6.5% and without experiencing confirmed hypoglycemia (70 mg/dL and 54 mg/dL as cut-off point).

Change in FPG is an acceptable secondary efficacy endpoint by regulatory agencies (15),(16) and scientific association. Change in 24-hour average plasma glucose, assessed as mean of 8 measurements in each 8-point SMPG profile, is an acceptable secondary efficacy endpoint by regulatory agencies. Lower diurnal fluctuation of glycemia in insulin-treated T2DM patients accounts for decrease in the frequency of episodes of hypoglycemia or hyperglycemia. The secondary endpoint of variability of plasma glucose is set up to assess if longer duration of action of the new formulation of insulin and less fluctuation in systemic exposure favorably affect variability of plasma glucose. The analysis will be based on self-monitored plasma glucose measurements (eg, 4-point and 8-point glucose profiles, fasting plasma glucose).

Safety evaluation will be evaluated by standard clinical and laboratory measurement, including the comparison of all hypoglycemia events occurrence frequency and distribution. Nocturnal hypoglycemia timeframe is defined as during standardized period (0:00 to 5:59 AM) and extended period (0:00 to 7:59 AM) and at sleep status to observe the hypoglycemia event when patients are usually at sleeping period, usually in fasting condition. Specific safety parameters of interest for a glucose lowering injectable peptide such as injection site reactions and hypersensitivity will also be assessed. Other TEAE will be evaluated and summarized.

Repeat assessment of PROs will be performed throughout the study (Including diabetes treatment satisfaction, perception of hypoglycemia and hyperglycemia questionnaires [DTSQs and DTSQc] and Hypoglycemia Attitudes and Behavior Scale [HABS]).

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

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

This is an outpatient study and consists of 9 on-site visits and 12 phone-call visits. Additional, optional phone call visits to monitor insulin titration should be scheduled whenever considered necessary by the investigator. All on-site visits should take place in the morning at approximately the same time (patient is in **fasting conditions** at Visit 1 (Week -2, screening visit), Visit 2 (Day 1, baseline), Visit 10 (Week 8), Visit 14 (Week 12), Visit 20 (Week 24), see also Study Flowchart, [Section 1.2](#)).

The **fasting condition** is defined as an overnight fast no less than 8 hours that consisted of no food or liquid intake, other than water. IMP and non-insulin antidiabetic medication should be administered after the fasting blood sample is drawn for all laboratory tests on the study site.

Note: If the patient is not in fasting conditions at visits which required in fasting conditions, the blood sample is not collected and a new appointment should be given to the patient for the following day if possible, with instruction to be fasted.

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

Visit window: From Visit 3 (Week 1) to Visit 9 (Week 7), a timeframe of ± 3 days is acceptable using the day of visit 2 (baseline) as reference (if one visit date is changed, the next visit should take place according to the original schedule). From Visit 10 (Week 8) up to the final primary endpoint assessment at Visit 20 (Week 24), a time frame of ± 5 days is acceptable. For Visit 21 (follow up visit) a time frame of -1~+3 day post-treatment is acceptable.

10.1.1 Screening period (Week -2 to Week 0)

Only patients who meet the inclusion criteria as noted in [Section 7.1](#) may be screened. It will be the investigator’s responsibility to confirm the diagnosis of T2DM.

All laboratory tests measured at a central laboratory that are needed for checking the exclusion criteria of the patients, are performed at the screening visit. At V2 (Day 1), patient who meet the selection criteria at the end of screening period as noted in [Section 7.2](#) can be randomized into on-treatment period.

All background non-insulin antidiabetic medications should be continued without dose and type change during screening period.

If any of the laboratory parameters are not available 2 weeks after screening visit (eg, sample material damaged during transport etc), a retest can be performed. As an exception, if justified according to the Investigator's assessment, the screening period can be extended one additional week, ie, baseline visit (V2, Day 1) can be scheduled no later than 3 weeks after screening visit (V1, Week -2).

Patients can be re-screened one time before randomization in case of non-evaluable exclusion criteria 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 (see below) including new informed consent signed and allocation of a new patient number.

10.1.1.1 Screening visit: V1 (Week-2)

For the complete list and contents of procedures/assessments scheduled for the visits, refer to the "Study Flow Chart" in [Section 1.2](#) and for detailed description of assessments to [Section 9](#) and [Section 10.6](#).

The details of the procedures/assessments to be performed at screening on-site visits and which are not described elsewhere are provided below:

Informed consent

The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration at the screening visit. Written information will be provided to the patient and must be signed by the patient and investigator prior to any investigations.

Demography, diabetes, medical/surgical, and allergy history, alcohol and smoking habits and medications

Demography data such as birth date, gender and race will be collected. Collection of diabetes history will include documentation of duration of diabetes, concomitant anti-diabetic medication; Medical/surgical history including patient's allergy history. Data for alcohol habits during the last 12 months before screening visit and smoking habit will be collected.

Check of previous or current medication (within the previous 3 months) refers to documentation of medication including the glucose-lowering agents (type and daily dose on the day before V1 should be recorded in e-CRF). In women of child-bearing potential, the contraceptive methods have to be documented in source document.

Diet and lifestyle counseling

Please see [Section 8.1](#).

IVRS/IWRS contact

IVRS/IWRS will be contacted for notification of screening and patient number allocation ([Section 8.5](#)). Please note that it is important to have the IVRS/IWRS contact before any blood sample is drawn because the patient number is given by IVRS/IWRS and it must be reported on the laboratory requisition forms.

Glucometer, diary dispensation and training

Please see [Section 9.2.1.2](#).

Central laboratory testing

- Blood sample is drawn for all central laboratory tests needed for checking the exclusion criteria.

A 12-lead electrocardiogram (ECG) will be performed locally at screening visit for identifying patients with exclusion criteria or safety consideration. The 12-lead ECGs should be performed after at least 10 minutes rest in supine position. All original traces are kept as source data.

From the signature of the informed consent form, AEs/SAEs (including the injection site reaction) will be recorded at each visit. Hypoglycemia and concomitant medications will also be recorded all along the study.

An appointment is given to the patient for next visit (on-site visit). Patients are instructed to return to the site in the morning and to bring the glucometer, the diary on next on-site visit (V2, Day 1) and instructed to perform 8-point SMPG over a single calendar day on at least one day in the 5 days prior to V2 (see [Section 9.2.1.2.2](#)).

10.1.2 Open-label randomized treatment period (Week 0 to Week 24)

Patients meeting all inclusion criteria and with no exclusion criteria at the end of the screening period are eligible to be enrolled into the open-label randomized treatment period. The duration of the open-label treatment period is 24 weeks \pm 5 days from baseline visit (V2, Week 0) to the end of treatment visit (V20, Week 24).

Each patient self-administers IMP once daily during the open-label treatment period. The IMP dose will be adjusted according to fasting SMPG values recorded in the glucometer ([Section 8.2.4](#)).

10.1.2.1 Baseline visit (V2, Week 0, Day 1)

For the complete list and contents of procedures/assessments scheduled for the visit, please refer to the “Study Flow Chart” in [Section 1.2](#) and for detailed description of assessments to [Section 9](#) and [Section 10.6](#).

The details of the procedures/assessments to be performed at this visit and which are not described elsewhere are provided below:

At this visit, the patient must return to the investigation site in the morning after **8 hours fasting** not having their non-insulin antidiabetic medication at home. Patients will visit the site with the blood glucometer and the diary.

Diet and lifestyle counseling

Please see [Section 8.1](#).

Compliance check

Compliance check includes compliance with use of glucometer, review of daily fasting SMPG values, and the **8-point SMPG profile** and patient diary. If patient is not compliant enough with the study procedures, the training will be repeated by the site staff.

IVRS/IWRS contact

After the baseline assessments are completed and eligibility confirmed, the investigator contacts IVRS/IWRS for randomization. The treatment group (ie, the Toujeo or Tresiba) is notified by IVRS/IWRS.

Training on self-injection devices and dispensation of IMP:

Patients randomized to the Toujeo group or Tresiba group are instructed by the study staff how to use properly the SoloStar disposable pen or FlexTouch disposable pen and to store it accordingly. Instructions on self-injection technique are also given. The instruction leaflet is dispensed. Training on the relevant pen injector might be repeated if necessary.

The Toujeo SoloStar(s) disposable pen and Tresiba FlexTouch disposable pen are dispensed according to randomized group for patients.

Please refer to [Section 8.2.2](#).

Starting dose and dose adjustment of IMP

Eligible patients will enter a 24-week open-label randomized treatment period to receive either Toujeo or Tresiba. Please see details in [Section 8.2.4](#).

An appointment for one week later is given to the patient for next phone call visit and two weeks later for next on-site visit.

10.1.2.2 On-Site Visits: V4 (Week 2); V6 (Week 4); V10 (Week 8); V14 (Week 12); V16 (Week 16); V18 (Week 20)

For the complete list and contents of procedures/assessments scheduled for the visits, please refer to the “Study Flow Chart” in [Section 1.2](#) and for detailed description of assessments to [Section 9](#) and [Section 10.6](#).

The details of the procedures/assessments to be performed at visits and which are not described elsewhere are provided below.

Compliance check

Compliance check includes compliance with IMP and non-insulin anti-diabetic medication treatment and use of glucometer, review of daily fasting SMPG values, and patient diary. If the patient is not sufficiently compliant with the study, the training has to be repeated by the site staff.

For on-site visits in V10 and V14 patients are instructed to return to the site in the morning in fasting condition. Patient will be instructed to perform 4-point and 8-point SMPG on the week before each correspondence visit (see [Section 1.2](#)). For all on-site visit, patients are instructed to bring the glucometer, the diary and the used/in-use/unused pens (V4, collecting used study medication only) and a re-supply of IMP is planned for all on-site visit (except V4).

Upon completion of each on-site visit, an appointment for the next visit (on-site visit or phone call visit) will be made.

10.1.2.3 Phone call Visits: V3 (Week 1); V5 (Week 3); V7, 8, 9 (Week 5, 6, 7); V11, 12, 13 (Week 9, 10, 11); V15 (Week 14); V17 (Week 18); V19 (Week 22)

The patient is called by the investigator or qualified designee at a scheduled time. If the call has been completed by site staff other than the investigator, the investigator has to be consulted if AE/SAE is suspected and informed in case AE/SAE occurred. In case of an AE, the patient may be asked to come to the investigational site, as appropriate. A phone call visit can optionally be performed as an on-site visit in case of symptomatic hypoglycemia/AE or other reasons.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you miss, change, take or add any medications (including non-insulin anti-diabetic medication if appropriate) since the last visit?
- Did you experience any symptoms or events of hypoglycemia?
- Do you feel comfortable handling the diary, glucose meter and IMP injection device or do you need any more explanation?
- Did you adjust IMP since last visit and reason? If appropriate, what is your IMP dose?
- Did you measure any fasting SMPG value outside of the range 80 to 100 mg/dL (4.4 to 5.6 mmol/L)?
- Did you experience any possible allergic symptom, or skin reaction?

The phone visits will also include:

- Asking patient fasting pre-breakfast SMPG and insulin dose on the last week including day of visit,
- Adjustment of the dose of IMP (insulin Toujeo and Tresiba) to continue treatment toward the target fasting SMPG between 100 and 80 mg/dL (5.6 and 4.4 mmol/L), inclusive,
- Recording of AE and symptomatic hypoglycemia events (if any),
- Recording of the use or change of any concomitant medication.

The patient will be instructed to:

- Perform required SMPG measurements,
- Complete daily the diary,
- Self-inject once daily IMP at the dose prescribed by the investigator between 6:00 PM and 8:00 PM,
- Contact the site in case of occurrence of adverse event, record the event in the patient's diary and return to the site as deemed appropriate.

Give an appointment to the patient for subsequent visits (on-site visit or phone call visit) and remind them to come in fasting condition if planned at next on-site visit and to bring their glucometer, diary, pens.

10.1.2.4 Final on-treatment assessment/end of treatment visit (V20, Week 24)

For the complete list and contents of procedures/assessments scheduled for the visit, please refer to the "Study Flow Chart" in [Section 1.2](#) and for detailed description of assessments to [Section 9](#) and [Section 10.6](#).

The same procedures/assessments including IVRS/IWRS contact as planned at Visit 20 (Week 24) have to be performed in case of prematurely permanent treatment discontinuation ([Section 10.3.2](#)). The IVRS/IWRS has to be contacted in order to register the end of treatment.

An appointment for the post-treatment follow-up phone call visit will be made (except for patients who prematurely discontinue the study treatment but continue in the study).

10.1.3 Post-treatment follow-up phone call visit (V21)

Following the last injection of insulin Toujeo or the Tresiba either as scheduled or prematurely, a post-treatment follow-up phone call visit is performed 7 (-1/+3) days after the end of treatment visit for patients who completed the study or withdrew from the study at the time of the open-label IMP discontinuation. The post-treatment follow-up phone call visit is not performed for patients who prematurely discontinued the open-label IMP treatment and stay in the study up to completion. This visit can be a phone call visit or an on-site visit in case of ongoing or new AE during the post-treatment period, if necessary.

The patient is called by the investigator or medically qualified designee at certain, previously agreed time point.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you change, take or add any new medications since the last visit?
- Did you experience any events or symptoms of hypoglycemia?

All reports of hypoglycemic events (if any) or any adverse events are recorded. The use or change of any concomitant medications, including rescue therapy, is recorded.

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in the patient's files

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

- Agreement and signature of informed consent mentioning the study identification
- Patient identification, last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology
- Contraception method for women of childbearing potential
- Reason for lack of childbearing potential for concerned women (eg, postmenopausal, history of hysterectomy)
- Previous and concomitant medication (including background anti-diabetic medication and rescue therapy)
- Study identification
- Treatment kit number, dates of administration and doses of the Toujeo or Tresiba alone
- Compliance to non-insulin anti-diabetic medication if appropriate assessed by interview and patient's diary
- Dates of visits and assessments including the examination report
- Vital signs, height, body weight
- Faxed central lab reports and original report received at site (dated and signed by the Principal Investigator or Sub-Investigator)
- IVRS/IWRS confirmation notifications by fax or e-mail (screening, screen failure, randomization, treatment allocation, treatment/study discontinuation, end of study, treatment replacement if applicable, etc)

- ECG records signed and dated

Adverse events and follow-up:

- In case of SAE, the site should file in the source document at least copies of the hospitalization reports and any relevant examination reports (eg, imaging reports, specialists' reports, etc) documenting the follow-up of the SAE or AESI
- Date of premature study discontinuation (if any) and reason

Source documentation may be found in the following:

- Patient's identity
- Medical history
- Nursing notes
- Dietician's notes
- Physician's notes
- Patient's diaries
- Dated and signed print-outs with SMPG downloaded from glucose meter

10.2.2 Source data verification requirements for patients not randomized

For patients not randomized, the source data that must be checked include the patient's identification details, the informed consent signed by the patient, the study identification, the dates of study visits and the main reasons preventing randomization.

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

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

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs or for other reason. In case of treatment interruption due to an AE, reinitiating 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 7.1](#) and [Section 7.2](#)).

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

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

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

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 8.9](#))

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

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol (except for the 7-day safety post-treatment follow up) 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 permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP (end of treatment visit).

For PRO assessments, please refer to [Section 9.3.1](#).

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF and in the patient's medical record when considered as confirmed. IVRS/IWRS should be notified when a patient prematurely discontinues treatment.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit.

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

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

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

In addition, the date of discontinuation of the study for patients who discontinued the IMP should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

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

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

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

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

- Results in death, or
- Is life-threatening, or
Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

- Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm
 - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
 - Convulsions (seizures, epilepsy, epileptic fit, absence seizure, etc).
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers, except non-melanoma skin cancer, diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study

10.4.1.3 Adverse event of special interest

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

All AESIs will be reported to the Sponsor in the same timeframe as SAEs, ie, within 24 hours as detailed in [Section 10.4.3](#).

The AESIs are listed below:

- Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see [Section 10.4.1.2](#)).
 - In the event of pregnancy in a female participant, IMP should be discontinued.
 - Follow-up of the pregnancy is mandatory until the outcome has been determined.
- 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 patient (not based on systematic drug count) and defined as follows
 - For IMP and other insulin: any dose administration which, in the investigator's opinion based on clinical judgment is considered significantly greater than the prescribed dose of insulin.
 - An overdose with non-insulin anti-diabetic medication is defined as at least twice of the intended dose within the intended/ planned therapeutic interval.

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

- Increase in alanine transaminase (ALT).

ALT ≥ 3 ULN (if baseline ALT < ULN) or ALT ≥ 2 times the baseline value (if baseline ALT \geq ULN) should be notified within 24 hours to the monitoring team (see [Section 10.4.4](#)). In addition, if ALT < 3 ULN meets a seriousness criterion, the event should be notified within 24 hours to the monitoring team.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to

IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).

- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
 - Symptomatic and/or
 - Requiring either corrective treatment or consultation, and/or
 - Leading to IMP discontinuation or modification of dosing, and/or
 - Fulfilling a seriousness criterion, and/or
 - Defined as an AESI

Instructions for AE reporting are summarized in [Table 3](#)

10.4.3 Instructions for reporting serious adverse events

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

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

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

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in [Section 10.4.3](#), even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

Instructions for AE reporting are summarized in [Table 3](#).

Table 3 - Summary of adverse event reporting instructions

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

Note: Hypoglycemia will be reported on the dedicated hypoglycemia event page. AESI: Adverse Event of Special Interest

10.5 OBLIGATIONS OF THE SPONSOR

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

- All SAEs those are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs those are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition (eg, blood glucose increased) and thus will not be considered unexpected as given in the Investigator's Brochure for Toujeo (3) and Product information for Tresiba (5).

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypoglycemia

Hypoglycemia events will be categorized as follows according to ADA category (17):

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

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

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

Documented symptomatic hypoglycemia

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration of ≤ 70 mg/dL (3.9 mmol/L).

Clinical symptoms that are considered to result from a hypoglycemic episode can include (but not necessarily limited to): increased sweating, nervousness, asthenia, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, and coma. Patients will be instructed to measure finger stick plasma glucose levels prior to the administration of carbohydrates whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose rescue prior to confirmation, and then a glucose measurement should be performed as soon as safe, with appropriate diary documentation. Details on hypoglycemia episodes will be captured in the patient diaries, and patients will contact the sites as soon as possible following severe events to review the details and decide on any necessary measures to be taken.

Asymptomatic hypoglycemia

Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L).

Probable symptomatic hypoglycemia

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

Pseudo hypoglycemia

Pseudo-hypoglycemia is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level.

Nocturnal hypoglycemia

Nocturnal hypoglycemia is any hypoglycemia of the above categories that occurs:

- Between 00:00 AM and 05:59 AM or 00:00 AM and 7:59 AM, regardless whether patient was awake or work up because of the event.
- Sleep status: patient was asleep between bedtime and before getting up in the morning, ie, before the morning determination of fasting pre-breakfast SMPG and patient woke-up due to the hypoglycemia

Note: **Confirmed hypoglycemia:** Any hypoglycemia confirmed by plasma glucose value below the cut off value (1) of 70 mg/dL (3.9 mmol/L) or (2) 54 mg/dL (3 mmol/L).

All hypoglycemia episodes will be documented on the dedicated hypoglycemia event page in the e-CRF. Symptomatic hypoglycemia events fulfilling the criteria of a SAE will also be documented on AE and SAE complementary forms in the e-CRF.

10.6.2 Local tolerability at injection site and hypersensitivity reactions

If the investigator or the patient recognizes any signs of local intolerability at the study drug injection site or hypersensitivity reactions, the event should be recorded in the adverse event page in the e-CRF. If a patient reports severe injection site or hypersensitivity reaction between the on-site visits or during a phone call visit, the investigator should ask him/her to come to the study site on the same or the next day, so that the event can be properly assessed, reported and treated.

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy variable of HbA1c change from baseline to Week 24.

A sample size of 920 randomized patients (460 randomized per treatment group) will ensure that the upper bound of the two-sided 95% confidence interval (CI) for the adjusted mean difference between Toujeo and Tresiba would not exceed a non-inferiority margin of 0.3% with at least 90% power. This calculation assumes a common SD of 1.4% with a 1-sided test at the 2.5% significant level and a true difference between Toujeo and Tresiba is zero in HbA1c between the treatment groups.

Calculations were made using nQuery Advisor[®] Software Version 7.0.

11.2 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be presented.

- Screened: all patients who originally met inclusion criteria and signed the informed consent
- Screen failure patients and reason for screen failure
- Randomized: all screened patients with a treatment arm allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not
- Safety population (see [Section 11.3.2](#)) presented as treated
- The intent-to-treat (ITT) population ([Section 11.3.1.1](#)) analyzed as randomized
- The randomization strata (screening HbA1c categories [$<8.0\%$, $\geq 8.0\%$], use of SU or meglitinides at screening [Yes, No]) assigned by IVRS/IWRS will be summarized. The discrepancy between the strata assigned by IVRS/IWRS and the information reported on CRF will be listed for all randomized patients
- The Per-Protocol (PP) population ([Section 11.3.1.2](#) analyzed as subset of ITT population and without major protocol deviations)
- Patients who permanently discontinued the IMP, and the reasons for permanent treatment discontinuation

For all categories of patients except screened and screen failure patients, percentages will be calculated using the number of randomized patients as denominator for different treatment groups.

Patients with the following deviations will be identified and described in separate listings:

- Treated but not randomized
- Randomized but not treated
- Randomized but not treated as randomized

A list of patients prematurely discontinued from the treatment, along with reasons for discontinuation, will be provided.

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

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent-to-treat population

The primary efficacy population will be the ITT population, which includes all randomized patients who received at least one dose of IMP, irrespective of the treatment actually being received, analyzed according to the treatment group allocated by randomization.

11.3.1.2 Per-protocol population

The per-protocol population is a subset of ITT population with no major protocol deviations. This is an efficacy population. Patients included in this population will fulfill at least the criteria below:

- Randomized and received only the treatment allocated at the randomization
- HbA1c value at baseline and at Week 24 on treatment
- Without initiating rescue therapy
- Who did not permanently discontinue treatment

The Per-protocol population will be fully defined in the SAP.

11.3.2 Safety population

The safety population is defined as all randomized patients who did actually receive at least one dose of IMP, regardless of the amount of treatment administered.

In the event of patients having received treatments that differed from those assigned according to the randomization schedule, then the safety analyses will be conducted according to the treatment received rather than according to the randomization groups.

Patients will not be considered exposed if there is documented evidence that patients have not taken the study drug:

- If a patient is dispensed IMP and is lost to follow-up without any documented evidence, the patient will be considered exposed and included in the safety population
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized

In addition:

- Non randomized but treated patients will not be part of the safety population, but their safety data will be presented separately
- For patients receiving more than one study treatment during the trial, the patient will be analyzed in the treatment group in which he/she was treated longer

11.3.3 PRO population

The analysis of PROs will be conducted on the ITT population.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

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

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

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

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will

also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- up to 4 weeks
- >4 to 8 weeks
- >8 to 12 weeks
- >12 to 16 weeks
- >16 to 20 weeks
- >20 to 22 weeks
- >22 to 23 weeks
- >23 to 24 weeks
- >24 weeks

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance percentage will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

11.4.2.1.1 Primary analysis

The primary efficacy variable, change in HbA1c from baseline to Week 24 in % as defined in [Section 9.1.1](#) will be analyzed in the ITT population using available data during the 24-week on treatment period (defined in [Section 9.2.1](#)). A mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out via SAS PROC MIXED using an adequate contrast at Visit 20 (Week 24).

The model will include fixed categorical effects of treatment group, visit, treatment-by-visit interaction, randomization stratum of use of SU or meglitinides at screening (Yes, No) as well as, the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction.

This model will be run with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least squares (LS)

means estimates at Week 24 for both treatment groups, as well as, the differences of these estimates, with their corresponding SEs and 95% CIs.

A stepwise closed testing approach will be used for the primary efficacy variable to assess non-inferiority and superiority sequentially detailed in [Section 11.4.2.3](#):

- Step 1 will proceed to assess non-inferiority Toujeo versus Tresiba. To assess non-inferiority, the upper bound of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to Week 24 between Toujeo and Tresiba will be compared with the predefined non-inferiority margin of 0.3% HbA1c. Non-inferiority will be demonstrated if the upper bound of the two-sided 95% CI of the difference between Toujeo and Tresiba on ITT population is $<0.3\%$.
- Step 2 will test superiority of Toujeo over Tresiba, only if non-inferiority of Toujeo versus Tresiba has been demonstrated. The superiority of Toujeo over Tresiba will be demonstrated if the upper bound of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to Week 24 between Toujeo over Tresiba on ITT population is <0 (zero).

The tests for the primary endpoint (Week 24) will be performed one-sided at level $\alpha = 0.025$.

11.4.2.1.2 Key sensitivity analysis

A first sensitivity analysis will be conducted in the ITT population, using all available post-baseline HbA1c values, regardless of study treatment discontinuation and rescue therapy initiation (analysis on the 24-week randomized period, as defined in [Section 9.1](#)). The same MMRM model as described for primary analysis will be used.

A second sensitivity analysis will be performed on the change in HbA1c from baseline to Week 24 in the Per-protocol population. The same MMRM model as described for primary analysis will be used.

11.4.2.1.3 Sensitivity analyses to handle missing data

Sensitivity analyses will be conducted to assess the robustness of primary efficacy analysis with regard to missing data.

Penalized multiple imputation

In order to assess the impact of missing data, the change in HbA1c from baseline to Week 24 in % using HbA1c values during the randomized 24-week period (all post baseline available data), will be analyzed in the ITT population using a multiple imputation approach to account for missing data at any time points (including missing baseline, Week 8, Week 12 and Week 24) followed by the testing of treatment arms using an analysis of covariance (ANCOVA) model.

Missing data will be imputed 100 times to generate 100 complete data sets with the MI SAS procedure. For each simulation leading to negative imputed value, another value will be redrawn

for imputation using MINIMUM option of MI SAS procedure. Since in general, the missing pattern will not be monotone, a two-step approach will be used:

- Step 1: the MCMC method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern
- Step 2: using the monotone data set from Step 1, missing data will be imputed using the regression method

The imputation model for Step 1 will include the treatment group, baseline HbA1c value, as well as HbA1c values at Week 8, Week 12, and Week 24.

The imputation model for Step 2 will include the same variables as in Step 1 with the randomization strata.

For each simulation leading to negative imputed value, another value will be redrawn for imputation using MINIMUM option of MI SAS procedure.

The imputed HbA1c value at Week 24 in the Toujeo group will then be penalized by adding 0.3% (corresponding to the non-inferiority margin) to the imputed HbA1c value whereas the imputed HbA1c in the Tresiba group will not be penalized. The change in HbA1c from baseline to endpoint will then be derived from observed and imputed (penalized or not) HbA1c value at Week 24.

The 100 complete data sets will then be analyzed using an analysis of covariance (ANCOVA) model including the fixed categorical effects of randomization stratum of screening HbA1c ($<8.0\%$, $\geq 8.0\%$), and randomization stratum of use of SU or meglitinides at screening (Yes, No), treatment group (Toujeo, Tresiba), as well as, the continuous fixed covariate of baseline HbA1c value. The MIANALYZE procedure will then be used to generate valid statistical inferences by combining results from the 100 analyses using Rubin's formulae.

This procedure will provide baseline adjusted least-squares means estimates at Week 24 for both treatment groups, as well as, the differences of these estimates, with their corresponding SEs and 95% CIs.

Tipping point analysis

Robustness of the primary analysis results to departure from the MAR assumption will be explored in the ITT population using tipping-point analysis based on the pattern mixture model approach.

The considered pattern mixture model will introduce a sensitivity parameter, δ , corresponding to the difference in means between patients with missing data and patients with observed data. Estimations will be performed using the same multiple imputation approach as described above. δ will be added to the imputed values ($\delta = 0$ corresponds to the MAR assumption). For each assessed value of δ by treatment group will correspond an estimated mean HbA1c reduction per group and an estimated treatment effect.

To investigate how the conclusions depend on the adopted values of δ , the testing will be repeated over a range of plausible values for the pairs (δ Toujeo, δ Tresiba). Results will be then summarized using graphs.

Further pattern mixture models could be explored depending on the observed missing data pattern in the Toujeo arm.

11.4.2.2 Analyses of secondary efficacy endpoints

Secondary efficacy endpoints are described in [Section 9.2](#)

All secondary efficacy endpoints will be analyzed or summarized on the 24-week on treatment period using the ITT population.

The following secondary efficacy endpoint will be analyzed using the same approach as the one used for primary endpoint (MMRM model) as described in [Section 11.4.2.1](#).

- HbA1c (%): change from baseline to Week 12;

The following secondary efficacy endpoints will be analyzed using the same approach as the one used for primary endpoint (MMRM model) as described in [Section 11.4.2.1](#). The model will include fixed categorical effects of treatment group, visit, treatment-by-visit interaction, randomization stratum of use of SU or meglitinides at screening (Yes, No), randomization stratum of HbA1c ($< 8.0\%$ and $\geq 8.0\%$), the continuous fixed covariates of the corresponding baseline value, and baseline value-by-visit interaction..

- FPG: change from baseline to Week 12 and Week 24;
- Fasting SMPG: change from baseline to Week 12 and Week 24;
- Change in 8-point SMPG profiles per time-point from baseline to Week 12 and Week 24;
- Change in 4-point SMPG profiles per time-point from baseline to Week 12 and Week 24;
- Change of mean 24-hour plasma glucose based on 8-point SMPG from baseline to Week 12 and Week 24;
- Change in variability of fasting SMPG and 24-hour plasma glucose based on 8-point SMPG from baseline to Week 12 and Week 24;
- Basal insulin dose(U and U/kg body weight): change from baseline to Week 12 and Week 24;

The following secondary endpoints will be analyzed using logistic regression model adjusted on randomization strata of screening HbA1c ($< 8.0\%$, $\geq 8.0\%$) and randomization strata of SU used at screening (yes/no). This model will also estimate the Odds Ratio of Toujeo and Tresiba and its corresponding 95% CI.

- Percentage (%) of patients reaching target HbA1c $< 7\%$ and $\leq 6.5\%$ at Week 12 and Week 24;

- Percentage (%) of patients reaching target HbA1c $<7\%$ and $\leq 6.5\%$ at Week 12 and Week 24 without severe and/or confirmed hypoglycemia (70 mg/dL and 54 mg/dL as cut off point) event during the 12 weeks treatment period and the 24 weeks treatment period;
- Percentage (%) of patients with SU or meglitinide dose reduction due to hypoglycemia;
- Percentage of patients requiring rescue therapy during 24 weeks treatment period

Hypoglycemia will be determined during the 12-week on-treatment period and the 24-week on-treatment period, respectively (used for Safety endpoint, as defined in [Section 11.4.3.1](#))

Patients who initiate rescue therapy during the 12-week on-treatment period or during the 24-week on treatment period, respectively, will be considered as failure for this given period.

Patients with missing HbA1c at a given visit will be considered as failure for this given visit.

The 24-week on treatment period as defined for Safety endpoint will be used (refers to [Section 9.2.2](#)).

11.4.2.3 Multiplicity considerations

To control the type I error, a hierarchical step-down testing procedure described by Hochberg and Tamhane (18) will be applied for the primary efficacy endpoint to assess non-inferiority and superiority sequentially (see [Section 11.4.2.1](#)).

- Step 1: non-inferiority comparison of the mean change from baseline to Week 24 in HbA1c with Toujeo compared to Tresiba
- Step 2: only if non-inferiority of Toujeo relative to Tresiba in step 1 is demonstrated, superiority of Toujeo over Tresiba in changes in HbA1c from baseline to Week 24 will be assessed

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

11.4.3 Analyses of safety data

11.4.3.1 Observation period of safety endpoints:

The observation period of safety data will be divided into 3 segments:

- The **pre-treatment period** is defined as the time between the date of signed informed consent and the first injection of open-label IMP
- The **on-treatment period** (24-week on-treatment period) is defined as the time from the first injection of open-label IMP up to 7 days after the last injection of open-label IMP, regardless of the introduction of rescue therapy. The 7-day interval is chosen based on the half-life of the IMP (approximately 5 times the half-life of Tresiba),

- 12-week on-treatment period is defined as the time from the first injection of IMP up to Week 12 or 7 days after the last injection of IMP whichever comes earlier.
- The **post-treatment period** is defined as the time starting 8 days after the last injection of open-label IMP (after on-treatment period).

The baseline value for safety endpoints will be the last available value prior to the first injection of open-label IMP.

11.4.3.2 Safety endpoints

Safety endpoints are described in [Section 9.2.2](#).

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

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

- The baseline value for safety endpoints will be the last available value prior to the first injection of IMP
- The following definitions will be applied to vital signs:
 - The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for vital signs
 - PCSA criteria will determine which patients had at least one PCSA during the TEAE period, taking into account all evaluations performed during the on-treatment TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage during the TEAE on-treatment period

11.4.3.2.1 Hypoglycemia

The number and incidence of patients experiencing at least 1 hypoglycemic event will be presented per treatment group and type of hypoglycemic event (ADA Workgroup on Hypoglycemia [17], [Section 10.6.1](#)) according to time of occurrence {nocturnal (ie, 00:00 to 05:59 AM; 00:00 to 07:59 AM), any time of the day} during the on treatment period. The Odds Ratio and its corresponding 95% CI of Toujeo arm over Tresiba arm for each hypoglycemic event will be estimated by a logistic regression model using the same approach as the one described for categorical efficacy endpoint.

The number and rate of hypoglycemic events (in patient-year of exposure) will be determined per treatment arm and type of hypoglycemic event (ADA Workgroup on Hypoglycemia [17]), according to time of occurrence {nocturnal (ie, 00:00 to 05:59 AM; 00:00 to 07:59 AM), any time of the day} during the on treatment period. For each hypoglycemic event, the rate ratio, and its corresponding 95% CI, of Toujeo arm over Tresiba arm will be estimated using an over-dispersed Poisson regression model adjusted on randomization strata of screening HbA1c (<8.0%, ≥8.0%) and randomization strata of SU or meglitinides at screening (Yes vs No).

The number and incidence of patients experiencing at least 1 nocturnal hypoglycemic event defined by sleep status and the number and rate of these nocturnal events (in patient-year of exposure) will also be presented per treatment group during the on treatment period.

11.4.3.2.2 Adverse events

All adverse events will be coded to a “PT” and “HLGT”, “HLT” and associated primary “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 system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order, and for each treatment arm, 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 arm.

Adverse event incidence table will be provided by titration modality arm for all types of TEAEs: all TEAEs, all treatment emergent SAEs, all TEAEs leading to permanent treatment discontinuation and all TEAEs related to local tolerability at injection site and hypersensitivity.

Death

The following deaths summaries will be generated on the safety population:

- Number (%) of patients who died by study period (TEAE, on-study, post-study*) and reasons for death summarized by allocated treatment arm
- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT

**Post-study deaths, if presented, will follow safety guideline instruction*

Injection site reaction and hypersensitivity reaction

Number (%) of patients with events related to injection site reactions or hypersensitivity reaction will be provided separately

Adverse event of special interest

A listing of patients with symptomatic overdose with IMP/NIMP and increase of ALT will be provided separately.

Patients with an SAE or AESI should be followed until resolution, stabilization, or death as appropriate.

Product technical complain (PTC)

Information regarding PTC will be described.

11.4.3.2.3 Vital signs and physical examination

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment arm whatever the baseline level and according to baseline status.

Change from baseline to Week 24 in body weight will be analyzed using the same approach as the one used to analyze FPG.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

Not applicable.

11.4.5 Analyses of Patient Reported Outcomes (Health-related Quality of Life/health economics variables)

The analysis of PROs will be conducted on the ITT population

PRO endpoints are described in [Section 9.3.1](#) .

For each questionnaire a descriptive summary at each visit (baseline, Week 12 and Week 24) and change from baseline at Week 12 and Week 24 (except for DTSQc) will be provided, excluding data obtained after rescue therapy initiation, including:

- DTSQs total treatment satisfaction score (items 1, 4, 5, 6, 7 and 8), ‘perceived frequency of hyperglycemia’ (Item 2) and ‘perceived frequency of hypoglycemia’ (Item 3) scores
DTSQc total treatment satisfaction score (items 1, 4, 5, 6, 7 and 8), ‘perceived frequency of hyperglycemia’ (Item 2) and ‘perceived frequency of hypoglycemia’ (Item 3) scores (at Week 12 and Week 24 only)
- HABS subscale scores (confidence, anxiety and avoidance)

The change in DTSQs and HABS scores from baseline to endpoint are analyzed using an MMRM model similar as model used for quantitative secondary efficacy endpoints.

Average scores at Week 12 and at Week 24 in total treatment satisfaction score, hyperglycemia perception and hypoglycemia perception score from DTSQc will be analyzed using an ANCOVA model. This model will include fixed categorical effects of treatment arm, on randomization strata of screening HbA1c (<8.0%, ≥8.0%) and randomization strata of SU used at screening (yes/no) as well as continuous fixed covariates of corresponding baseline score from DTSQs.

11.5 INTERIM ANALYSIS

No interim analysis will be performed during the study.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

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

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

12.2 INFORMED CONSENT

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

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

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

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

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

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

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

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, serious adverse event (SAE) documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized

personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

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

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

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

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

13.5 USE OF COMPUTERIZED SYSTEMS

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

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

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

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

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

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

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

14.3 CONFIDENTIALITY

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

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

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

14.6 INSURANCE COMPENSATION

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

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

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

In case of substantial amendment to the clinical trial protocol, approval from the Health Authorities (Competent Regulatory Authority) will be sought before implementation.

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

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