STATISTICAL ANALYSIS PLAN

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

HOE901 - LPS14584

STATISTICIAN: [redacted]

BIOSTATISTICS PROJECT LEADER : [redacted]

DATE OF ISSUE: 03-Jul-2017

NCT02738151

Total number of pages: 77

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN **1**

TABLE OF CONTENTS **2**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS **5**

1 OVERVIEW AND INVESTIGATIONAL PLAN **7**

1.1 STUDY DESIGN AND RANDOMIZATION 7

1.2 OBJECTIVES 7

1.2.1 Primary objectives 7

1.2.2 Secondary objectives 8

1.3 DETERMINATION OF SAMPLE SIZE 8

1.4 STUDY PLAN 9

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL 13

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN 13

2 STATISTICAL AND ANALYTICAL PROCEDURES **14**

2.1 ANALYSIS ENDPOINTS 14

2.1.1 Demographic and baseline characteristics 14

2.1.2 Prior or concomitant medications 16

2.1.3 Efficacy endpoints 18

2.1.3.1 Primary efficacy endpoint(s) 19

2.1.3.2 Secondary efficacy endpoint(s) 19

2.1.4 Safety endpoints 20

2.1.4.1 Hypoglycemia events 21

2.1.4.2 Adverse events variables 22

2.1.4.3 Deaths 23

2.1.4.4 Laboratory safety variables 23

2.1.4.5 Vital signs variables 24

2.1.4.6 Electrocardiogram variables 24

2.1.5 Pharmacokinetic variables 24

2.1.6 Pharmacodynamic/genomics endpoints 25

2.1.7 Patient-reported outcome endpoints 25

2.1.8 Health economic endpoints 26

2.2 DISPOSITION OF PATIENTS 26

2.2.1 Randomization and drug dispensing irregularities 28
2.3 ANALYSIS POPULATIONS 28
2.3.1 Efficacy populations 29
2.3.1.1 Intent–to-treat population 29
2.3.1.2 Per-protocol population 29
2.3.2 Safety population 30
2.3.3 PRO population 30
2.4 STATISTICAL METHODS 30
2.4.1 Demographics and baseline characteristics 30
2.4.2 Prior or concomitant medications 31
2.4.2.1 Non-anti-diabetic medication 31
2.4.2.2 Anti-diabetic medication 32
2.4.3 Extent of investigational medicinal product exposure and compliance 33
2.4.3.1 Basal insulin dose 33
2.4.3.2 Extent of investigational medicinal product exposure 33
2.4.3.3 Compliance 33
2.4.4 Analyses of efficacy endpoints 34
2.4.4.1 Analysis of primary efficacy endpoint(s) 34
2.4.4.2 Analyses of secondary efficacy endpoints 39
2.4.4.3 Summary of results per time point 41
2.4.4.4 Multiplicity issues 41
2.4.4.5 Additional efficacy analysis 42
2.4.4.6 Analyses of exploratory efficacy endpoints 43
2.4.5 Analyses of safety data 43
2.4.5.1 Analyses of hypoglycemia 44
2.4.5.2 Analyses of adverse events 47
2.4.5.3 Deaths 50
2.4.5.4 Analyses of laboratory variables 50
2.4.5.5 Analyses of vital sign variables 50
2.4.5.6 Analyses of electrocardiogram variables 51
2.5 DATA HANDLING CONVENTIONS 51
2.5.1 General conventions 51
2.5.2 Data handling conventions for secondary efficacy variables 53
2.5.3 Missing data 56
2.5.4 Windows for time points 59
2.5.5 Unscheduled visits 61
2.5.6 Pooling of centers for statistical analyses 61
2.5.7 Statistical technical issues 61
3 INTERIM ANALYSIS 62

4 DATABASE LOCK 63

5 SOFTWARE DOCUMENTATION 64

6 REFERENCES 65

7 LIST OF APPENDICES 66

APPENDIX A. POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA 67

APPENDIX B. ANTI-DIABETIC DRUG ATC CODES 71

APPENDIX C. HYPOGLYCEMIA CLASSIFICATION (ADA/FDA) SCHEMA 72

APPENDIX D. THE DIABETES TREATMENT SATISFACTION QUESTIONNAIRE STATUS VERSION (DTSQS) 73

APPENDIX E. THE DIABETES TREATMENT SATISFACTION QUESTIONNAIRE CHANGE VERSION (DTSQC) 74

APPENDIX F. HABS (HYPOGLYCEMIA ATTITUDES AND BEHAVIOR SCALE) 75

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	american diabetes association
AE(s):	adverse event(s)
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferases
ANCOVA:	analysis of covariance
AST:	aspartate aminotranferases
ATC:	anatomic therapeutic chemical
BMI:	body mass index
CI:	confidence interval, confidence interval
CRF:	case report form
DBP:	diastolic blood pressure
DTSQ:	diabetes treatment satisfaction questionnaire
DTSQc:	diabetes treatment satisfaction questionnaire change version
DTSQs:	diabetes treatment satisfaction questionnaire status version
ECG:	electrocardiogram
e-CRF:	electronic case report form
FPG:	fasting plasma glucose
FSH:	follicle stimulating hormone, serum follicle stimulating harmone
GFR:	glomerular filtration rate
GLP-1:	glucagon like peptide-1
HABS:	hypoglycemic attitudes and behavior scale, hypoglycemic attitudes and behavior scale
HbA1c:	glycated hemoglobin A1c
HLGT:	high-level group term
HLT:	high-level term
IMP:	investigational medicinal product
ITT:	intent-to-treat
IVRS:	interactive voice response system
IWRS:	interactive web response system
LLT:	lower-level term
LS:	least square
MAR:	missing at random
MCMC:	markov chain Monte Carlo
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
MMRM:	mixed-effect model with repeated measures
NIMP:	non-investigational medical product
OADs:	oral antidiabetic drugs
PCSA:	potentially clinically significant abnormalities

PRO(s):	patient reported outcome(s)
PT:	preferred term , preferred term
SAE(s):	serious adverse event(s)
SAS:	statistical analysis system
SBP:	systolic blood pressure
SD:	standard deviation
SEs:	standard error
SMPG:	self-monitored plasma glucose
SMQ:	standardized medDRA query
SOC:	system organ class
SU:	sulphonylurea
T2DM:	Type 2 Diabetes mellitus
TEAE(s):	treatment-emergent adverse event(s)
ULN:	upper limit of normal
WHO-DD:	world health organization-drug dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a 24-week, multinational, multicenter, randomized, open-label, 2-arm parallel-group trial, Phase IV study comparing Toujeo® to Tresiba®.

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

- Toujeo (Insulin Glargine 300U) group
- Tresiba (Insulin Degludec 100U) group

Patients will receive in a 1:1 ratio either Toujeo or Tresiba.

A total of 920 patients (460 in Toujeo group and 460 in Tresiba group) are expected to be randomized from approximately 165 sites.

The randomization will be stratified by value of glycated hemoglobin A1c (HbA1c) obtained at the screening visit (<8.0%; ≥8.0%) and sulphonylurea (SU) or meglitinides use before the day of screening (Yes; No).

The type and dose of antidiabetic 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 investigational medicinal product [IMP]) or identified safety concerns necessitate a reduction in dose or discontinuation of non-insulin antidiabetic drug(s).

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the 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-naive patients with Type 2 Diabetes mellitus (T2DM) not adequately controlled with Oral Antidiabetic Drugs (OADs) with or without GLP-1 receptor agonist.

1.2.2 Secondary objectives

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.
  - Change in variability of fasting SMPG and 24-hour plasma glucose over Week 12 and Week 24.
  - Percentage of patients reaching HbA1c targets <7% or ≤6.5% at Week 12 and Week 24.
  - Percentage of patients reaching HbA1c targets <7% or ≤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).
  - Hypoglycemic Attitudes and Behavior Scale (HABS).

1.3 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) ensures 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 standard deviation (SD) of 1.4% with a 1-sided

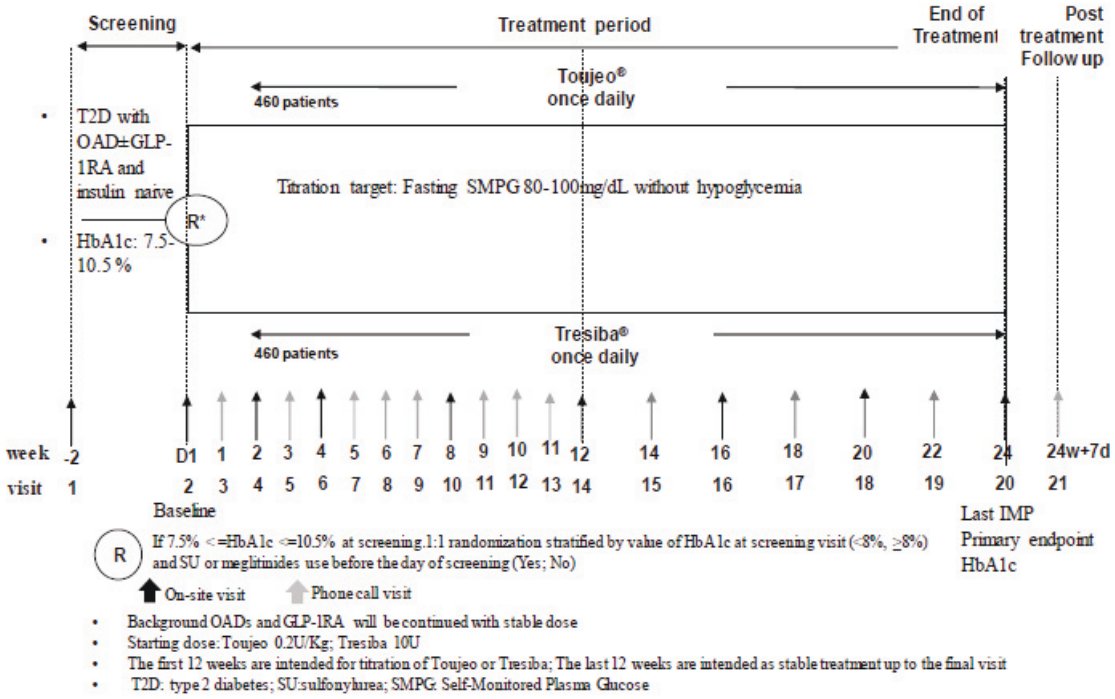
test at the 2.5% significant level and a true difference between Toujeo and Tresiba is zero in HbA1c between the treatment groups.

Calculations were made using nQuery Advisor® Software Version 7.0.

1.4 STUDY PLAN

The following figure describes the design of the study:

Figure 1 – Graphical study design



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.

In total the maximum study duration will be approximately 27 weeks per patient:
2 weeks + 24 weeks + 7 days.

For all patients who prematurely and permanently discontinue the study treatment, assessments scheduled at the “End of treatment visit”, will be performed as soon as possible. Afterward, the patients should continue in the study up to the scheduled date of study completion.

For patients who completed the study or withdrew from the study at the time of the prematurely and permanently IMP discontinuation, the “Post-treatment safety follow up visit” is performed 7-days after the end of treatment visit. The “Post-treatment safety follow up visit” is not performed for patients who prematurely discontinued the IMP and stay in the study up to completion.

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.

Patients with an SAE or an adverse event (AE) with pre-specified monitoring will be followed until resolution, stabilization or death.

The following table describes the study flow chart.

Table 1 – 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	
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 antihypergycemic 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

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The statistical section of the protocol was never changed in an amendment.

The protocol history table below gives the timing, rationale and key details of major changes to the protocol statistical section.

Amendment Number	Date Approved	Rationale	Description of statistical changes
NA	NA	Modification of basal insulin dose (U and U/kg body weight) analysis	MMRM analysis for the change from baseline to Week 12 and Week 24 of basal insulin dose will be replaced by a descriptive analysis.
NA	NA	Modification of basal insulin doses section	Basal insulin dose was included in the Section 2.4.3.1
NA	NA	Modification of analysis in 8-point SMPG profiles per time-point	MMRM analysis for the change in 8-point SMPG profiles per time-point from baseline to Week 12 and Week 24 was removed. Only a descriptive analysis will be performed.
NA	NA	Modification of analysis in 4-point SMPG profiles per time-point	MMRM analysis for the change in 4-point SMPG profiles per time-point from baseline to Week 12 and Week 24 was removed. Only a descriptive analysis will be performed.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

There was no Statistical Analysis Plan amendment.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value prior to the first injection of open-label IMP.

For randomized and not treated patient, the baseline value is defined as the last available value obtained up to the date and time of randomization.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

- Age (years),
- Age qualitative categories: <65, ≥65 years
- Gender (Male, Female),
- Baseline body weight (kg),
- Baseline body weight (kg: <50, ≥50 and <100, ≥100 kg,
- Baseline Body Mass Index (kg/m^2),
- Baseline body mass index (BMI) categories (kg/m^2): <30, ≥30 – 35<, ≥35 kg/m^2,
- Baseline estimated glomerular filtration rate ([GFR], using modification of diet in renal disease [MDRD] formula, mL/min/1.73m^2),
- Baseline estimated glomerular filtration rate (GFR, using MDRD formula, mL/min/1.73m^2) : <15 End stage, ≥15 and <30 Severe decrease, ≥30 and <60) Medium decrease, ≥60 and <90) Mild decrease, ≥ 90 Normal,
- Randomization strata of screening HbA1c categories (<8.0; ≥8.0%),
- Randomization strata of Sulphonylurea (SU) or meglitinides use before the day of screening (Yes; No).

Medical or surgical history

Medical / surgical history includes patient's allergy history.

This information, pre-listed or not in the e-CRF, will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

Specific disease history includes:

- Duration of diabetes (years),
- Category of duration of diabetes (<10, ≥10 years),
- Age (years) at onset of diabetes,
- Previous non-insulin antihyperglycemic treatment:
  - Duration of previous non-insulin antihyperglycemic treatment (years),
  - Previous non-insulin antihyperglycemic treatment (yes /no),
  - Number of previous non-insulin antihyperglycemic agent (0, 1, 2 ,>2),
  - Previous non-insulin antihyperglycemic treatment (biguanides, sulfonylurea, glinides, thiazolidinediones, DDP-4 inhibitors, SGLT-2 inhibitors, GLP1-RA, alpha-glucosidase inhibitors, other),
- Diabetic microvascular complications (yes or no):
  - Diabetic retinopathy (yes/no/unknown), photocoagulation performed (yes/no/unknown) and vitrectomy performed because of diabetic retinopathy (yes/no/unknown),
  - Diabetic neuropathy (yes/no/unknown),
  - Diabetic nephropathy (yes/no/unknown) including the most recent event categories (microalbuminuria, overt proteinuria or impaired renal function).

Baseline efficacy data

The following baseline efficacy data will be provided:

- HbA1c (% and mmol/mol),
- FPG (mmol/L and mg/dL),
- Mean of SMPG (mmol/L and mg/dL) from 8-point profiles measured on a 24-hour period, and SMPG per time-point,
- Average pre-breakfast SMPG (mmol/L and mg/dL) = mean of pre-breakfast (fasting).

SMPG values in the last 7 days prior the 1st IMP (see Section 2.5.2).

Other baseline efficacy endpoints are presented along with the summary statistics.

Basal insulin at baseline

Basal insulin daily dose (U and U/kg): Is equal to the actual starting IMP dose of basal insulin as reported by the investigator into the e-CRF (first IMP intake).

Smoking/alcohol habits

- Tobacco habits (never, quit smoking, currently smokes) including the average number of cigarettes per day,
- Alcohol habits (never, at least monthly, at least weekly, at least daily) including the number of daily standard drink (1 or 2, > 2).

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

Other baseline characteristics (such as quality of life/health economic endpoints) are presented along with the summary statistics.

2.1.2 Prior or concomitant medications

All medications taken within the past 3 months before screening and until the end of the study are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used within 3 months and from screening to first investigational medicinal product (IMP) intake. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from first injection of IMP to the last injection of IMP+7 days (0 day for antidiabetic therapy). A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in Section 2.1.4).
- Post-treatment medications are those the patient continued or started on or after 8 days (1 day for antidiabetic therapy) after the last dose of open-label IMP.

Anti-diabetic medication will be identified by a pre-defined list of anatomic therapeutic chemical (ATC) codes (see in Appendix B).

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

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 explains 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.

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 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.

2.1.3 Efficacy endpoints

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

HbA1c and FPG are measured at a central laboratory, for scheduled (see study flowchart in Table 1) and unscheduled time points.

Patients measure their SMPG using the blood glucometer and document them into the diary. The following SMPG values are copied in the eCRF (see study flowchart in Table 1).

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).

In case of premature permanent IMP discontinuation or rescue therapy intake, the process described in Section 2.5.4 will be applied to retrieve efficacy assessments performed at the end of treatment visit or at pre-rescue visit.

Observation period of efficacy endpoints

- **The 24-week on-treatment period** (used to assess the on-treatment estimand) for efficacy endpoints (primary and secondary efficacy endpoints) is defined as the time from the first injection dose of open-label IMP up to:
  - 7 days after date of last IMP administration for HbA1c, or up to the introduction of the rescue therapy, whichever is earlier for the patient,
  - 0 day after date of last IMP administration for 4-point and 8-point SMPG and insulin dose, or up to the introduction of the rescue therapy, whichever is earlier for the patient,
  - 1 day after date of last IMP administration for FPG and fasting SMPG, or up to the introduction of the rescue therapy, whichever is earlier for the patient,
  - 2 days after date of last IMP administration for hypoglycemia or up to the introduction of rescue therapy, whichever is earlier for the patient,
- **The randomized 24–week period** (used to assess the intent-to-treat [ITT] estimand) for efficacy variables is defined from first dose of IMP up to Week 24, (visit 20), regardless of study treatment discontinuation and intake of rescue therapy.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy variable is the change in HbA1c from baseline (scheduled day 1) to Week 24 which is defined as: HbA1c value at Week 24 – HbA1c value at baseline (%).

Results for primary efficacy endpoint will also be presented in mmol/mol.

2.1.3.2 Secondary efficacy endpoint(s)

Secondary efficacy endpoints are:

- Change in HbA1c (mmol/mol and %) from baseline to Week 12,
- Change in FPG (mmol/l and mg/dL) from baseline to Week 12 and Week 24,
- Change in fasting SMPG (mmol/l and mg/dL) from baseline to Week 12 and Week 24,
- Change in 4-point SMPG (mmol/l and mg/dL) profiles per time-point from baseline to Week 4, Week 8, Week 12 and Week 24,
- Change in 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 (mmol/l and mg/dL) from baseline to Week 12 and Week 24,
- Change in variability of fasting SMPG from baseline to Week 12 and Week 24,
- Change in variability of 24-hour plasma glucose based on 8-point SMPG (mmol/l and mg/dL) 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% at Week 24 without severe and/or confirmed hypoglycemia (≤70 mg/dL) during the 24 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c <7% at Week 24 without severe and/or confirmed hypoglycemia (<54 mg/dL) during the 24 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c <7% at Week 12 without severe and/or confirmed hypoglycemia (≤70 mg/dL) during the 12 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c <7% at Week 12 without severe and/or confirmed hypoglycemia (<54 mg/dL) during the 12 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c ≤6.5% at Week 24 without severe and/or confirmed hypoglycemia (≤70 mg/dL) during the 24 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c ≤6.5% at Week 24 without severe and/or confirmed hypoglycemia (<54 mg/dL) during the 24 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c ≤6.5% at Week 12 without severe and/or confirmed hypoglycemia (≤70 mg/dL) during the 12 weeks treatment period,

- Percentage (%) of patients reaching target HbA1c ≤6.5% at Week 12 without severe and/or confirmed hypoglycemia (<54 mg/dL) during the 12 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.

Any technical details related to computation and imputation for missing data are described in section 2.5.

2.1.4 Safety endpoints

The safety analysis will be based on:

- All hypoglycemia events (according to American Diabetes Association [ADA] Workgroup on Hypoglycemia),
- Local tolerability at injection site,
- Hypersensitivity reactions,
- Adverse events with special interest (AESI) with immediate notification:
  - Increase in alanine aminotransferases (ALT);
  - Pregnancy;
  - Symptomatic overdose with IMP/NIMP;
- Other adverse events (AE) or serious adverse events (SAEs),
- Vital signs including body weight.

In case of premature permanent IMP discontinuation or rescue therapy intake, the process described in Section 2.5.4 will be applied to retrieve safety assessments performed at the end of treatment visit or at pre-rescue visit.

Observation period for 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 signed informed consent and the first injection of open-label IMP.

- **The on-treatment period (24-week on-treatment period / 24-week TEAE period**) is defined as the time from the first injection of open-label IMP up to 7 days (or 2 days for hypoglycemia) 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 (12-week TEAE period)** is defined as the time from the first injection of IMP up to Week 12 or 7 days (or 2 days for hypoglycemia) after the last injection of IMP whichever comes earlier.
- **The post-treatment period** is defined as the time starting 8 days (or 3 days for hypoglycemia) 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.

The on-study observation period is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

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

2.1.4.1 Hypoglycemia events

All hypoglycemia events will be categorized as follows according to ADA category (1):

- Severe hypoglycemia: an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. 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: an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L);
- Asymptomatic hypoglycemia: an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L);
- Severe and/or confirmed hypoglycemia by a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L): any hypoglycemia event of the three above categories;
- Probable symptomatic hypoglycemia: 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 ≤70 mg/dL (3.9 mmol/L); symptoms treated with oral carbohydrate without a test of plasma glucose;

- Pseudo-hypoglycemia: 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.

Hypoglycemia observation periods

- **Pre-treatment hypoglycemia events** are events that occur during the pre-treatment period,
- **Treatment-emergent hypoglycemia events** are events that occur during the 24 Week on-treatment period,
  - **12 week Treatment-emergent hypoglycemia events** are events that occur during the 12weeks on-treatment period;
- **Post-treatment hypoglycemia events** are events that occur during the post-treatment period.

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

- Daytime hypoglycemia: any hypoglycemia of the above categories that occurs:
  - Between 06:00 and 23:59.
- Nocturnal hypoglycemia: any hypoglycemia of the above categories that occurs:
  - Between 00:00 and 05:59 am, regardless whether patient was awake or woke up because of the event.
  - Between 00:00 and 7:59 am, regardless whether patient was awake or woke 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.
- At any time of the day distributed by 2-hour of the day (0:00-23:59).

In addition of the threshold of ≤70 mg/dL (3.9 mmol/L), hypoglycemia episodes with plasma glucose <54 mg/dL (3.0 mmol/L) will be analysed.

2.1.4.2 Adverse events variables

All adverse events (including serious adverse events and adverse events with special interest) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

The occurrence of adverse events (including serious adverse events and adverse events with special interest) is recorded from the time of signed informed consent until the end of the study.

Adverse event observation period

- Pre-treatment adverse events are adverse events that developed or worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the TEAE period (as defined in the observation period in Section 2.1.4).
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period.

Injection site reaction adverse events are identified using MedDRA searches: HLGT "Administration site reactions" and HLTs "Administration site reactions NEC" , "Infusion site reactions", "Injection site reactions" and "Application and instillation site reactions" and excluding HLTs "Implant and catheter site reactions" and "Vaccination site reactions".

Hypersensitivity reactions adverse events are identified using MedDRA searches: Angioedema SMQ [Narrow], Severe cutaneous adverse reactions SMQ [Broad], Hypersensitivity SMQ [Broad and Narrow] and excluding PTs related to administration, application, injection and infusion sites. HLT "Anaphylactic Responses"are included in those SMQs

Adverse events of special interest include:

- 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.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP.
- Increase (≥3 ULN or >2 times the baseline value) in alanine transaminase (ALT).

2.1.4.3 Deaths

The deaths observation period are per the observation periods defined above:

- Death on-study: deaths occurring during the on study observation period.
  - Death pre-treatment: deaths occurring before the first IMP intake;
  - Death on-treatment: deaths occurring during the treatment-emergent adverse event period;
- Death post-study: deaths occurring after the end of the study.

2.1.4.4 Laboratory safety variables

Clinical laboratory data consists 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 after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken 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. The laboratory parameters will be classified as follows:

- Hematology,
  - **Red blood cells and platelets**: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, red blood cell count, platelet count, prothrombin time (expressed as international normalized ratio), activated partial thromboplastin time, sedimentation rate;
  - **White blood cells**: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils;
- Clinical chemistry,
  - **Electrolytes**: sodium, potassium,;
  - **Renal function**: creatinine, eGFR;
  - **Liver function**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase (ALP), total and conjugated bilirubin;
  - **Pregnancy test**: Serum β-human chorionic gonadotropin (all female patients);
- Urine samples will be collected as follows:
  - **Urinalysis** - quantitative analyses: pH, specific gravity, proteins, and glucose.

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

Vital signs include: heart rate (bpm), sitting systolic and diastolic blood pressure (mmHg) as well as body weight (kg).

2.1.4.6 Electrocardiogram variables

Electrocardiogram variables include electrocardiogram (ECG) status (normal, abnormal not clinically significant, abnormal clinically significant).

2.1.5 Pharmacokinetic variables

Not applicable.

2.1.6 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.7 Patient-reported outcome endpoints

The patient reported outcomes (PROs) measures in this study are the Diabetes Treatment Satisfaction Questionnaire (DTSQs and DTSQc versions) and the Hypoglycemic Attitudes and Behavior Scale (HABS).

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. It consists of 8 items that are answered on a Likert scale from 0 to 6.(2)

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. 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.(3)..

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 hypoqlycemia' (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. (4).

The questionnaire will be administered at baseline, 12 and 24 weeks in the local language.

2.1.8 Health economic endpoints

Not applicable.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

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

Randomized patients consist of all screened patients with a treatment arm allocated and recorded in the interactive voice response system (IVRS)/ interactive web response system (IWRS) database, regardless of whether the treatment kit was used or not.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients;
- Screen failure patients and reasons for screen failure;
- Non-randomized but treated patients;
- Randomized patients;
- Randomized but not treated patients;
- Randomized and treated patients;
- Patients who completed the 24-week on-treatment period (patients who have performed visit 20, who did not permanently discontinue treatment and who did not take any rescue medication);
- Patients who did not complete the 24-week on-treatment period;
- Patients who discontinued 24-week on-treatment by main reason for permanent treatment discontinuation;
- Patients who completed the study (patients who have performed visit 20, whatever the treatment duration);
- Patients who did not complete the study (patients who have not performed visit 20);
- Patients who discontinued study by main reason for study discontinuation;

- The randomization strata (screening HbA1c categories [<8.0%, ≥8.0%], use of SU or meglitinides at screening [Yes, No]) assigned by IVRS/IWRS. The discrepancy between the strata assigned by IVRS/IWRS and the information reported on case report form (CRF) will be listed for all randomized patients;
- Status at last study contact.

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as denominator for different treatment groups. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group.

Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. A listing of patients who prematurely discontinued study treatment with further reason provided in free text will be provided.

Kaplan-Meier (KM) plots/estimates of the cumulative incidence of IMP discontinuation due to any reason will be provided. Time to treatment discontinuation is defined as the number of days from the first dose of IMP until the day of treatment discontinuation. All completers are considered as censored observations. The censoring time is the number of days from the first dose of IMP until the last dosing date.

Kaplan-Meier (KM) plots/estimates of the cumulative incidence of IMP discontinuation due to adverse event will be provided. Time to treatment discontinuation is defined as the number of days from the first dose of IMP until the day of treatment discontinuation. All completers are considered as censored observations. The censoring time is the number of days from the first dose of IMP until the last dosing date.Kaplan-Meier (KM) plots/estimates of the cumulative incidence of study discontinuation due to any reason will be provided. Time to study discontinuation is defined as the number of days from the randomization date until the day of study discontinuation. All completers are considered as censored observations. The censoring time is the number of days from the randomization date until the last visit date.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group. Patients excluded from the ITT/PP population will be listed as well as patients with major deviation potentially impacting efficacy analyses not resulting in exclusion from ITT or PP populations. These deviations are listed in the data review and surveillance plan.

Additionally, the analysis populations (Section 2.3) for safety and efficacy are summarized in a table by patient counts on the randomized population:

- Efficacy populations: ITT population; Per-Protocol population,
- Safety population.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Forced randomization
Stratification error
Patient switched to another site

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population.

Patients who are dispensed study drug without calling the IVRS or before calling the IVRS are considered non-randomized patients. They are excluded from any population for analysis,

including safety. However, if these patients experienced any significant safety event, they should be documented separately in the clinical study report.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

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.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population.

2.3.1.1 Intent–to-treat population

The intent-to-treat population 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.

2.3.1.2 Per-protocol population

The per-protocol population is a subset of the ITT population with no major / critical deviations. 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,
- HbA1c value at Week 24 on treatment,
- Without initiating rescue therapy,
- Who did not permanently discontinued treatment,
- With I01 Adult patients with T2DM inadequately controlled with OADs therapy with/without GLP-1 receptor agonist at stable dose for at least 3 months,
- Without E01 HbA1c <7.5% or >10.5% (at screening),
- Without E04 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,
- Without E15 The conditions/situations may interfere the evaluation for efficacy endpoints,
- Without used prohibited medication.

2.3.2 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:

- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately,
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized,
- 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.

2.3.3 PRO population

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

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum for each treatment group. For insulin dose and PROs, summary statistics will include quartiles Q1, Q3 and medians. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Similar analyses will be done on the ITT population in the as-randomized treatment group (respectively, PP population, safety population in the as-treated

treatment group) and will be included in the appendices if the size of the ITT population (respectively, PP population and safety population) is different (>10%) from the size of the randomized population for any treatment group. In the randomized population, parameters will also be summarized within each randomization stratum as per IVRS.

Medical/surgical history will be classified into primary system organ class (SOCs) and HLTs using MedDRA and will be summarized by treatment groups. Events will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on incidence in the overall treatment group.

P-values on demographic and baseline characteristic data will not be calculated.

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

No specific description of the efficacy parameters will be provided at baseline. If relevant, the baseline values will be described along with each efficacy analysis.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the randomized population.

Prior medication will be presented by treatment arm and overall whereas concomitant and post treatment medication will be presented by treatment arm.

2.4.2.1 Non-anti-diabetic medication

Non anti-diabetic medications will be summarized by treatment arm according to the WHO-DD dictionary, considering the first digit of the anatomic category (Anatomical Therapeutic Chemical [ATC]) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category).

All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for non-anti-diabetic prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for non-anti-diabetic concomitant and post treatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the Toujeo® group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

An individual listing sorted by treatment arm and subject number will be populated instead of summary table only if few non-antidiabetic either prior or post treatment medications are observed.

2.4.2.2 Anti-diabetic medication

Antidiabetic medications will be summarized by treatment arm according to the WHO-DD dictionary considering the pharmacological class (ATC3), chemical class (ATC4) and standardized medication name.

The table for antidiabetic prior medications will be sorted by decreasing frequency of pharmacological class followed by chemical class and standardized medication name based on the overall incidence across treatment arm. In case of equal frequency, alphabetical order will be used.

The tables for antidiabetic concomitant and post treatment medications will be sorted by decreasing frequency of pharmacological class followed by chemical class and standardized medication name based on the incidence in Toujeo treatment arm. In case of equal frequency, alphabetical order will be used.

In addition, the following specific medications will be summarized:

- The anti-diabetic concomitant rescue medication will be presented by pharmacological class, chemical class and standardized medication name.
- The prohibited concomitant medication will be presented by prohibited medication category as defined in deviation and standardized medication name.

A list of ATC codes to be used in determining these medications is in Appendix B.

Prior, concomitant and post-treatment antidiabetic non-insulin therapy and rescue will also be summarized per predefined classification and standardized medication name:

- Biguanides
- SU
- Glinides
- Thiazolidinedione
- DPP-4 inhibitors
- SGLT-2 inhibitors
- GLP1-RA
- Alpha-glucosidase inhibitors
- Other.

The numbers and percentages of patients in each level will be presented by treatment group.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment received within the safety population. (Section 2.3.2).

2.4.3.1 Basal insulin dose

Descriptive statistics of basal insulin dose (U and U/kg) will be presented including change from baseline, relative, change from baseline and change from previous visit.

For change in daily basal insulin at each visit and at endpoint (Week 12 and Week 24), a determination of the average daily insulin doses is made by using daily doses computed on a weekly basis. At each post-baseline visit, the mean daily basal insulin doses will be calculated as the mean of daily insulin doses collected over the last 7 days before the visit. No minimum number of available doses will be required.

In case of any missed doses, corresponding days should not be taken into account in the determination of the average daily insulin doses. In case of premature discontinuation or use of rescue medication, the average daily dose taken into consideration for a patient is the one measured the week before such event.

2.4.3.2 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of IMP exposure is defined as last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data). 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 and > 24 weeks.

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

2.4.3.3 Compliance

No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as the number of days with at least one administration divided by the duration of IMP exposure.

Treatment compliance will be summarized descriptively (N, Mean, SD, Median, Min and Max). The percentage of patients with compliance will be summarized for the classes ≤60%, >60 and ≤80, >80%.

Cases of overdose (provide definition as per protocol) will constitute adverse events and will be listed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

For statistics where international and conventional units do not impact the results (eg, means and least square (LSLS) means for percent changes from baseline, p-values for both percent and absolute changes from baseline, rates of patients below a threshold), derivations will be done and statistical models will be run using conventional units. For other statistics (eg, descriptive statistics at baseline and over time, absolute changes from baseline), derivations will be done with both international and conventional units.

Figures will be provided with 2 different axes by parameter when applicable. For example, for HbA1c, figures will be presented by % and mmol/mol.

2.4.4.1 Analysis of primary efficacy endpoint(s)

2.4.4.1.1 Primary efficacy analysis

The primary efficacy variable, change in HbA1c from baseline to Week 24 in % as defined in Section 2.1.3.1 will be analyzed in the ITT population using available data during the 24-week on treatment period (defined in Section 2.1.4, used to assess the on-treatment estimand). 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 (Toujeo, Tresiba), visit (Week 8, Week 12, Week 24), 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 standard error (SEs) and 95% CIs.

This analysis will be performed using the randomization strata as per IVRS.

A stepwise closed testing approach will be used for the primary efficacy variable to assess non-inferiority and superiority sequentially detailed in Section 2.4.4.3:

- 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 $\alpha = 0.025$. P-value will be provided.

Model assumption checks

The analysis of the residuals of MMRM will be based on studentized residuals. It includes:

- Normality of studentized residuals, presented graphically using histogram and QQ-plot
- Plot of studentized residuals versus predicted values.
- Distribution of studentized residuals, presented graphically using boxplots, within each category of the fixed categorical effects of the MMRM:
  - treatment group (Toujeo, Tresiba),
  - visit (Week 8, Week 12 and Week 24),
  - treatment-by-visit interaction,
  - randomization stratum of use of SU or meglitinides at screening (yes, no).

2.4.4.1.2 Subgroup analyses

Where appropriate for the size of a subgroup, exploratory analyses are performed on the primary endpoint to summarize the treatment effects across subgroups.

For each subgroup, the primary efficacy variable will be analyzed in the ITT population using post-baseline HbA1c data available on the 24-week on treatment period, (to assess the on-treatment estimand). A similar MMRM approach as described for primary analysis will be applied adding the corresponding subgroup factor, subgroup factor-by-treatment interaction, subgroup factor-by-visit interaction and subgroup factor-by-visit-by treatment interaction.

The subgroups will be defined by the following baseline and screening factors:

- Age group (<65 and ≥65 years of age),
- Gender (male, female),
- Baseline BMI (<30; ≥30 and<35; ≥35 kg/m²),
- Randomization stratum of screening HbA1c (<8.0%, ≥8.0%),
- Randomization stratum of use of SU or meglitinides at screening (yes, no),
- Number of previous non-insulin anti-hyperglycemic agent (0, 1, 2, >2),
- Previous non-insulin anti-hyperglycemic treatment at screening: GLP-1RA (yes/no),
- Previous non-insulin anti-hyperglycemic treatment at screening: DPP-4 inhibitor (yes/no),
- Previous non-insulin anti-hyperglycemic treatment at screening: SGLT-2 inhibitor (yes/no),
- Duration of diabetes (<10, ≥10 years),
- Baseline estimated GFR categories (mL/min/1.73m²): (<15; [15-30[; [30-60[; [60-90[; ≥90).

If the subgroup factor is a randomization stratification factor, then the strata as per IVRS will be used.

The randomization strata of screening HbA1c and use of SU or meglitinides at screening will not be included in the model.

Least Square Means Difference versus Tresiba at Week 24 will be provided, as well as the corresponding SEs and 95% CI, within each subgroup. The significance level of the treatment-by-subgroup factor interaction term at Week 24 will also be provided for each factor for descriptive purpose. Forest plots will be provided.

Subgroups analyses using randomization strata derived as per electronic case report form (e-CRF), should be performed only if necessary (in case of high number of discrepancies between stratum as per IRT and stratum as per e-CRF) and should be considered as sensitivity analysis.

Further subgroup analyses may be performed if deemed necessary for interpretation of results.

2.4.4.1.3 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, to assess the ITT estimand). 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 (analysis on 24-week on treatment period, to assess the on-treatment estimand). The same MMRM model as described for primary analysis will be used.

2.4.4.1.4 Sensitivity analyses to handle missing data

Sensitivity analyses will be conducted to assess the robustness of primary efficacy analysis with regard to missing data.(5). .

D***escription of missing data***

Missing data in the primary efficacy analysis (analysis on 24-week on treatment period, to assess the on-treatment estimand).

The following analyses will be performed on the ITT population to explore the missing data frequency and pattern in the primary efficacy analysis:

In order to explore missing data patterns for HbA1c in the primary efficacy analysis, number and percentage of patients in each of the following categories will be presented by treatment group:

- Pattern 1: patients without baseline if any,
- Pattern 2: patients with baseline but without post-baseline value during the 24-week on-treatment period,
- Pattern 3: patients with baseline and at least one post-baseline value during the 24-week on treatment period but not at Week 24,
- Pattern 4: patients with baseline and Week 24 value during the 24-week on-treatment Period.

Missing data in the key sensitivity efficacy analysis

The following analyses will be performed on the ITT population to explore the missing data frequency and pattern in the key sensitivity analysis:

In order to explore missing data patterns for HbA1c in the key sensitivity analysis, number and percentage of patients in each of the following categories will be presented by treatment group:

- Pattern 1: patients without baseline if any (ITT estimand),
- Pattern 2: patients with baseline but without post-baseline value (ITT estimand),
- Pattern 3: patients with baseline and at least one post-baseline value but not at Week 24 (ITT estimand),
- Pattern 4: patients with baseline and Week 24 value (ITT estimand).

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, to assess the ITT estimand (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 markov chain Monte Carlo (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 includes the same variables as in Step 1 with the randomization strata.

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 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 (δ = 0 corresponds to the missing at random [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.

2.4.4.1.5 Sensitivity to randomization strata

In order to assess the robustness of the primary analysis to randomization stratum errors, ie, the stratum recorded in IVRS differs from the actual one), the MMRM model will be re-run including the actual stratum as per the e-CRF instead of the stratum recorded in IVRS.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Analyses of secondary efficacy endpoints

Secondary efficacy endpoints are described in Section 2.1.3.2.

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

The following secondary efficacy endpoint will be analyzed using the same model (same analysis) as the one used for primary endpoint (MMRM model) as described in Section 2.4.4.1.1.

- 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 2.4.4.1.1.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 ≥ 8.0%), the continuous fixed covariates of the corresponding baseline value, and baseline value-by-visit interaction.

For the model on change FPG, the visit term has 3 levels (Week 8, Week 12 and Week 24).

For the models on Fasting SMPG data, the visit term has 7 levels (Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24).

For the models on 8-point SMPG data, the visit term has 7 levels (Week 12 and Week 24).

- FPG: change from baseline to Week 12 and Week 24;
- Fasting SMPG: change 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 from baseline to Week 12 and Week 24;
- Change in variability of 24-hour plasma glucose based on 8-point SMPG from baseline to Week 12 and Week 24.

The following secondary endpoints will be analyzed using descriptive measures as described in Section 2.4.4.1.1:

- 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 4, Week 8, Week 12 and Week 24.

Basal insulin dose (U and U/kg body weight): change from baseline to Week 12 and Week 24 (see Section 2.4.3.1);

The following secondary endpoints will be analyzed using logistic regression model adjusted on randomization strata of screening HbA1c (<8.0%, ≥8.0%) and randomization strata of SU or meglitinides 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 ≤6.5% at Week 12 and Week 24,
- Percentage (%) of patients reaching target HbA1c <7% at Week 24 without severe and/or confirmed hypoglycemia (≤70 mg/dL) during the 24 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c <7% at Week 24 without severe and/or confirmed hypoglycemia (<54 mg/dL) during the 24 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c <7% at Week 12 without severe and/or confirmed hypoglycemia (≤70 mg/dL) during the 12 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c <7% at Week 12 without severe and/or confirmed hypoglycemia (<54 mg/dL) during the 12 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c ≤6.5% at Week 24 without severe and/or confirmed hypoglycemia (≤70 mg/dL) during the 24 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c ≤6.5% at Week 24 without severe and/or confirmed hypoglycemia (<54 mg/dL) during the 24 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c ≤6.5% at Week 12 without severe and/or confirmed hypoglycemia (≤70 mg/dL) during the 12 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c ≤6.5% at Week 12 without severe and/or confirmed hypoglycemia (<54 mg/dL) during the 12 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 efficacy endpoint, as defined in Section 2.1.3).

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 (non-responders) for this given visit.

2.4.4.3 Summary of results per time point

Central laboratory values (in conventional (US) and international units), percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units), for HbA1c and FPG at Week 8, Week 12, Week 24, time points, will be summarized in the ITT population using:

- For HbA1c and FPG: LS mean and SE for each treatment group, obtained from the same MMRM models as used for endpoints above and including all planned time points and with raw values, changes from baseline, or percent change from baseline as response variable in the model as appropriate.

In addition, quantitative descriptive summaries by time point (value at visit and % change from baseline) will be presented for all variables using observed (ie, non-missing) data. In addition binary variables for HbA1c will also be described by time point.

And for other parameters bellow:

- Fasting SMPG,
- Change of mean 24-hour plasma glucose based on 8-point SMPG,
- Change in variability of fasting SMPG,
- Change in variability of 24-hour plasma glucose based on 8-point SMPG.

LS mean and SE for each treatment group, obtained from the same MMRM models as used for endpoints above and including all planned time points and with raw values, changes from baseline as response variable in the model as appropriate.

In addition, for all parameters quantitative descriptive summaries by time point (value at visit) will be presented for all variables using observed (ie, non-missing) data.

2.4.4.4 Multiplicity issues

To control the type I error, a hierarchical step-down testing procedure described by Hochberg and Tamhane will be applied for the primary efficacy endpoint to assess non-inferiority and superiority sequentially (see Section 2.4.4.1).

- 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.

2.4.4.5 Additional efficacy analysis

Patient Reported outcomes

All PROs will be analyzed using the ITT population.

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 (sum of 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 (sum of items 1, 4, 5, 6, 7 and 8), “perceived frequency of hyperglycemia” (Item 2) and “perceived frequency of hypoglycemia” (Item 3) scores (atWeek 12 and Week 24 only)
- HABS confidence score (items 4, 6, 8, 11 and 14), anxiety score (items 2, 5, 7, 9 and 12) and avoidance score (items 1, 3, 10 and 13).

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.

The change in DTSQs and HABS scores from baseline to endpoint are analyzed using a cumulative distribution functions of scores. Changes from baseline will be displayed by treatment groups, for each the 3 DTSQs/HABS scores and a graphical presentation will be used to illustrate trends over time per treatment arm by visit on mean scores ± √2 SE and on change from baseline values ± √2 SE.

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%), randomization strata of SU or Meglitinides used at screening (yes/no), as well as continuous fixed covariates of corresponding baseline score from DTSQs.

Cumulative distribution function of week 24 scores will be plotted by treatment arm for each of the 3 DTSQc scores.

For interpretation of results, Effect Sizes (ES) using Cohen's definition will be calculated in order to interpret changes from baseline to Week 12 and Week 24 in PRO scores.

- Within ES: calculated at the treatment group level, when focusing on changes from baseline
- Between ES: Calculated when comparing treatment groups

The calculation of interpretation of ES are described on Section 2.5.1.

2.4.4.6 Analyses of exploratory efficacy endpoints

Subgroup analyses by baseline estimated GFR categories (mL/min/1.73m²): <60; ≥60 will be performed on the following endpoints:

- Percentage (%) of patients reaching target HbA1c <7% at Week 24 without severe and/or confirmed hypoglycemia (≤70 mg/dL) during the 24 weeks treatment period,
- Percentage (%) of patients reaching target HbA1c <7% at Week 24 without severe and/or confirmed hypoglycemia (<54 mg/dL) during the 24 weeks treatment period,
- Change of fasting SMPG from baseline to Week 24,
- Change in variability of fasting SMPG from baseline to Week 24.

2.4.5 Analyses of safety data

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

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately,
- The baseline value is defined as the last available value prior to the first injection of IMP,
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal vital signs values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, (PCSA version 3 dated May 2014 [Appendix A]),
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations.

The number of all such patients will be the numerator for the on-treatment PCSA percentage,

- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population,
- For quantitative safety parameters based on reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the last on-treatment value. The last on-treatment value is defines as the value collected at the same day/time of the last dose of investigational product. If this value is missing, this on-treatment value is the closest on prior to the last dose intake,
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

2.4.5.1 Analyses of hypoglycemia

All safety analyses of hypoglycemia events will be performed by treatment group in the safety population on events occurring during the TEAE period (as described in Section 2.1.4):

- Percentage (%) of patients with at least one hypoglycemia event will be presented for any hypoglycemia and for each hypoglycemia category of time: any time, nocturnal, daytime (as described in Section 2.1.4.1). 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.
- Percentage (%) of patients with at least one hypoglycemia event will be presented for any hypoglycemia and for each hypoglycemia category of time: any time, nocturnal, daytime (as described in Section 2.1.4.1), excluding hypoglycemia occurring after the initiation of rescue therapy.
- Percentage (%) of patients with at least one hypoglycemia event, will be presented by study period (for ≤12 weeks, for >12 weeks to ≤24 weeks and during 24 weeks treatment period) for any hypoglycemia and for each hypoglycemia category (as described in Section 2.1.4.1). 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.
- Percentage (%) of patients with at least one hypoglycemia event, will be presented by study period (for ≤12 weeks, for >12 weeks to ≤24 weeks and during 24 weeks treatment period) for any hypoglycemia and for each hypoglycemia category (as described in Section 2.1.4.1) excluding hypoglycemia occurring after the initiation of rescue therapy.
- Percentage (%) of patients with at least one severe hypoglycemia event will be summarized by symptom during 24 weeks treatment period),

- Number and rate of hypoglycemia event per patient-year will be summarized for any hypoglycemia and for each hypoglycemia category (as described in Section 2.1.4.1). 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),
- Number and rate of hypoglycemia event per patient-year will be summarized for any hypoglycemia and each hypoglycemia category (as described in Section 2.1.4.1), excluding hypoglycemia occurring after the initiation of rescue therapy,
- Number and rate of hypoglycemia event per patient-year will be summarized by study period (for ≤12 weeks, for >12 weeks to ≤24 weeks and during 24 weeks treatment period) for any hypoglycemia and each hypoglycemia category (as described in Section 2.1.4.1), except probable and pseudo). Non classified hypoglycemia will be displayed. 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 versus No).

For Hypoglycemic ADA categories, in addition of threshold ≤70 mg/dL (3.9 mmol/L), hypoglycemia episodes with plasma glucose <54 mg/dL (3.0 mmol/L) will be analyzed.

For each type of Hypoglycemia: Cumulative number and rate hypoglycemia event per 100 patient-days will be summarized by time of the day. Figures will be provided.

Cumulative mean number of hypoglycemia will be summarized over time using Nelson-Aalen estimates. Figures will be provided.

In addition, to help the interpretation of the results, an exploratory analysis defined as risk difference could be performed.

Subgroups analyses

The proportion of patients with at least one:

- Severe and/or confirmed (≤3.9 mmol/L [≤70 md/dL]) hypoglycemia,
- Severe and/or confirmed (<3.0 mmol/L [<54 md/dL]) hypoglycemia.

during the 24-week on-treatment period, will also be presented by the following subgroups:

- Age group (<65 and ≥65 years of age),
- Gender (male, female),
- Baseline BMI (<30; [30 – 35[; ≥35 kg/m²),
- Randomization stratum of screening HbA1c (<8.0%, ≥8.0%),
- Randomization stratum of SU or meglitinides at screening (Yes vs No).

- Number of previous non-insulin anti-hyperglycemic agent (0, 1, 2, >2)
- Previous non-insulin anti-hyperglycemic treatment at screening , GLP-1RA (yes/no),
- Previous non-insulin anti-hyperglycemic treatment at screening: DPP-4 inhibitor (yes/no),
- Previous non-insulin anti-hyperglycemic treatment at screening: SGLT-2 inhibitor (yes/no),
- Duration of diabetes (<10, ≥10 years),
- Baseline estimated GFR categories (mL/min/1.73m²): (<15; [15-30[; [30-60[; [60-90[; ≥90),

and analyzed using a similar logistic regression model approach as presented previously, but adding the corresponding subgroup factor and treatment arm-by-subgroup interaction factor. Odds ratio estimates and 95% CI will be provided in each subgroup category.

The interaction treatment arm-by-subgroup p-value will be provided for descriptive propose.

When the subgroup considered is equal to one of the randomization strata or is part of one of the adjustment factor, this randomization stratum/adjustment factor is removed from the model.

If the logistic regression model does not converge (eg, due to sparse data) some of the randomization strata may be removed.

Forest plots will be provided.

Further subgroup analyses may be performed if deemed necessary for interpretation of results.

In addition the following analyses will be performed by Baseline estimated GFR categories (mL/min/1.73m²): <60; ≥60:

- proportion of patients with at least one nocturnal (00:00-07:59am) severe and/or confirmed (≤70 mg/dL) hypoglycemia,
- proportion of patients with at least one nocturnal (00:00-07:59am) severe and/or confirmed (<54 mg/dL) hypoglycemia.

Relative Risks

For any hypoglycemic category of event (see in Section 2.1.4.1) except pseudo and probable, the estimated proportions along with their corresponding 95% CI, as well as the relative risk of Toujeo arm versus Tresiba arm and their corresponding 95% CI, will be estimated by the mean of a log-binomial regression model, using a log-link function and a binomial response distribution, and stratified on:

- randomization stratum of use of SU or meglitinides at screening (Yes, No),
- randomization stratum of HbA1c (< 8.0 % and ≥ 8.0%)

This analysis will be done only for hypoglycemia event occurring at any time of the day.

Risk difference

For each hypoglycemic category of event (see in Section 2.1.4.1) except relative and probable, the adjusted risk differences of Toujeo arm versus Tresiba arm and their corresponding 95% CI, will be estimated by the mean of a log binomial regression model, with an identity link function and a binomial response distribution, and stratified on:

- randomization stratum of use of SU or meglitinides at screening (Yes, No),
- randomization stratum of HbA1c (< 8.0 % and ≥ 8.0%).

This analysis will be done only for hypoglycemia event occurring at any time of the day.

Scatter plots

Scatter plots of Relative Risk versus Risk Difference presenting each type of analyzed hypoglycemia for patient experiencing at least one hypoglycemia event:

- during 24 weeks on-treatment period
- occurring at any time of the day.

2.4.5.2 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

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

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and post-treatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the

presentation order for all other tables unless otherwise specified. Sorting will be based on results for the Toujeo® treatment arm.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any,
  - Treatment-emergent adverse event;
  - Serious treatment-emergent adverse event;
  - Treatment-emergent adverse event leading to death;
  - Treatment-emergent adverse event leading to permanent treatment discontinuation.
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order,
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified,
- All treatment-emergent adverse events (PT ≥5% in any treatment group incidence) by primary SOC and PT, showing the number (%) of patients with at least 1 treatment emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC,
- All common treatment-emergent adverse event (HLT incidence ≥ 2% in any treatment group) by primary SOC, HLT, and PT, showing number (%) of patients with at least 1 common treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLT, PT) will be presented in alphabetical order,
- All treatment-emergent adverse events regardless of relationship and related to IMP by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order,
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse

event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order,

- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

Analysis of injection site reactions and hypersensitivity reaction TEAE(s)

- All treatment-emergent adverse events related to injection site reactions or hypersensitivity reactions, by PT, showing the number(%) of patients sorted by decreasing incidence of PTs in Toujeo®.

Analysis of adverse events of special interest

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

Analysis of pretreatment and post-treatment adverse events

- All pre-treatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs in Toujeo ® within each SOC,
- All pre-treatment adverse events leading to study discontinuation by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs Toujeo ® within each SOC,
- All post-treatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs Toujeo ® within each SOC,
- All post-treatment serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment serious adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs Toujeo ® within each SOC,
- Listing of SAE,
- Listing of AEs leading to permanent treatment discontinuation.

2.4.5.3 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment, post-study,
- Deaths in non-randomized patients or randomized but not treated patients,
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC,
- All pre-treatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC,
- All post-treatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC,
- Listing of deaths.

2.4.5.4 Analyses of laboratory variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline) by treatment group. This section will be organized by biological function as specified in Section 2.1.4.4.

Drug-induced liver injury

The liver function tests, namely aspartate aminotranferases (AST), alanine aminotransferases (ALT) and total bilirubin, are used to assess possible drug-induced liver toxicity at the baseline visit and will be displayed by treatment group for each parameter.

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters: conjugated and non-conjugated bilirubin, creatine phosphokinase, serum creatinine.

Summarize the incidence of liver-related adverse events by treatment group. The number (%) of patients with events reported on the AE form for ALT increase and it is associated complementary forms will be summarized by PT.

2.4.5.5 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables blood pressure, heart rate and body weight (and changes

from baseline) will be calculated for each visit or study assessment (baseline, each post baseline time point, last on-treatment) by treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing,
- Abnormal according to PCSA criterion or criteria.

The change in body weight from baseline to Week 24 will be analyzed in the safety population using a similar MMRM model as described in Section 2.4.4.1.1.

Exploratory analyses will be performed for the body weight as follow:

- Change in body weight from baseline to week 24 for patients with Randomization strata (as per IRT): SU or Meglitinides = Yes,
- Change in body weight from baseline to week 24 for patients with Randomization strata (as per IRT): SU or Meglitinides = No.

using a similar MMRM model as described in Section 2.4.4.1.1. Randomization strata: SU or Meglinitides at screening will be removed from the model.

2.4.5.6 Analyses of electrocardiogram variables

Description at baseline only for ECG according to the following baseline status categories:

- Normal/missing,
- Abnormal, not clinically significant,
- Abnormal, clinically significant.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Reference day

The reference day for the calculation of extent of exposure, time to onset and relative days is the day of the first administration of IMP, denoted as Day 1.

Demographic formulas

Body Mass Index (kg/m^2) = (Weight in kg)/(Height in meters)^2.

Disease characteristics formulas

Duration of diabetes (years) = (Date of informed consent – date of diagnosis of diabetes +1)/365.25.

Age at onset of diabetes (years) = (Date of diagnosis of diabetes – date of birth +1) /365.25.

Duration of previous non-insulin anti-hyperglycemic treatment (years) = (Date of informed consent - date of first dose of previous non-insulin anti-hyperglycemic treatment +1) /365.25.

HbA1c transformation

To transform HbA1c in % to mmol/mol, the following formula is used:

IFCC = (10.93*NGSP) - 23.50

NGSP (National Glycohemoglobin Standardization Program network) corresponds to HbA1c (%) and IFCC (International Federation of Clinical Chemistry network) to HbA1c (mmol/mol)

FPG and SMPG conversion

From mg/dL to mmol/L: x 0.0555
From mmol/L to mg/dL: x 18.0148

Renal function formulas

No derivation because gender is not reported on e-CRF, so only central lab has this information.

Rate of hypoglycemia event per patient-year

Computed as [sum of number of episodes of hypoglycemia for all patients] / [sum of patient-year of exposure for all patients] with patient-year of exposure calculated per patient as number of days of exposure divided by 365.25.

Rate of hypoglycemia event per patient-year per study period:

- For ≤12 weeks: [sum of the number of episodes of hypoglycemia for all patients during the first 12 weeks] / [sum of patient-year of exposure for all patients during ≤12 weeks], with the patient-year of exposure during ≤12 weeks calculated as the number of days exposed during ≤12 weeks divided by (12x7),
- For >12 weeks to ≤24 weeks: [sum of the number of episodes of hypoglycemia since week 12 until week 24] / [sum of patient-year of exposure for all patients since week 12 until week 24], with the patient-year of exposure since week 12 until week 24 calculated as the number of days exposed since week 12 until week 24 (included) divided by (12x7),
- During 24 weeks: [sum of the number of episodes of hypoglycemia for all patients during 24 weeks of treatment period] / [sum of patient-year of exposure for all patients during 24 weeks of treatment period divided by (24x7).

2.5.2 Data handling conventions for secondary efficacy variables

Fasting condition

FPG measurement not collecting in fasting condition will not be used in the analyses.

Invalid laboratory data

HbA1c or FPG measurements flagged as invalid by the laboratory will not be used in the analyses.

HbA1c target

HbA1c target missing data handling

- Patients with missing HbA1c data at respectively Week 12 and Week 24 will be regarded as not having reached the HbA1c target (ie, as failure) at each given time-point.

Composite endpoints missing data handling

- For each cases presented above regarding missing HbA1c values the patient will be considered as failure for each composite endpoint of the corresponding randomized period,
- For each case presented above regarding missing hypoglycemia event information the patient will be regarded as failure for each related composite endpoint,
- In case of premature end of study during the 24 weeks randomized period the patient will be considered as failure for each composite endpoint relative to the 24 weeks period.

Change in HbA1c category

Patients with missing:

- Baseline HbA1c will be regarded as not having reached the HbA1c target at Week 12 and Week 24,
- HbA1c data at respectively at Week 12 and Week 24 will be regarded as not having reached the HbA1c target at each given time-point.

HABS

The Hypoglycemic Attitudes and Behavior Scale consists of 14 items within 3 domains measuring anxiety (5 items), confidence (5 items) and avoidance (4 items) related to hypoglycemia. The 3 domain scores are determined by computing the mean of item responses. At least 2/3 of the items should be completed for the calculation of each domain score, which means only one item missing is acceptable to calculate each domain score. If more than one item is missing, the domain score is considered as missing.

DTSQc and DTSQs

The total treatment satisfaction score is the sum of items 1, 4, 5, 6, 7 and 8.

If no more than 2 out of the 6 questions comprising the total treatment satisfaction score are missing, the total treatment satisfaction score is imputed by calculating the average of the scores from the answered questions, dividing this sum by the number of answered questions and multiplying the average by six.

If items 2 or 3 are not answered, frequency of hypoglycemia or hyperglycemia scores is considered as missing.

- In- between scores

  If a patient answers in-between response choices (eg, between 1 and 2), the score will be coded as 1.5.

- If a question is answered twice
  - If the scores that have been circled are next to each other (ie, 2 & 3), then the mid-point between them will be taken (ie, 2.5) as this is unlikely to be a mistake and more likely to represent difficulty in choosing a score.
  - However, if the two answers are not immediately next to each other (ie, 2 and 5 on the DTSQ, or 3 and 0 on the DTSQc), answers will be considered as missing.

Table 2 – Unexpected Scoring

Scoring issues	DTSQs	DTSQc
In between score	If patients answer in between choices, score should be coded as mean of both scores (i.e.: if between 2 and 3 coded 2.5)	
Item answered twice using 2 consecutive scores	Midpoint score should be used (ie,: if 1 and 2 are answered should be coded 1.5)	
Item answered twice but using non-consecutive scores	Score is set to missing	
Item is circled but accompanied by word	Only score should be taken into account	
If respondent as circle word of the extremes of the scale instead of value	Score should be the nearest value (ie,: 0 or 6)	Score should be the nearest value (ie,: -3 or 3)

Table 3 – PRO Missing Data Handling

PRO scales	Score	Number of items included in score derivation	Minimum number of items required for score calculation
HABS	Anxiety score	5	4
	Confidence score	5	4
	Avoidance score	4	3
DTSQs	Total treatment satisfaction score	6	4
	Perceived frequency of hyperglycemia score	1	1
	Perceived frequency of hypoglycemia score	1	1
DTSQc	Total treatment satisfaction score	6	4
	Perceived frequency of hyperglycemia score	1	1
	Perceived frequency of hypoglycemia score	1	1

Effect Size

The effect size is defined as: ES= difference/SD where SD is the standard deviation.
Note that there are two main types of effect size:

- Within ES: Calculated at the group level, when focusing on change from baseline
- Between ES: Calculated when comparing treatments groups

The within-group ES (WES) indicates if the changes from baseline to the end of treatment are clinically meaningful for each group.

$$\text{WES} = \frac{\textit{LS mean change from baseline at timepoint t}}{\textit{pooled baseline standard deviation}}$$

The between-group ES (BES) indicates if the mean changes from baseline to the end of treatment are clinically meaningful between groups.

$$\text{BES} = \frac{\textit{difference in LS means between groups at timepoint t}}{\textit{pooled baseline standard deviation}}$$

Cohen's rules for Effect Size (ES) and interpretation
ES >0.2 : Negligeable
0.2 ≤ ES <0.5 : Small
0.5 ≤ ES <0.8 : Moderate
ES ≥0.8 : Important

Handling of missing data in the calculation of the percentage of patients reaching a pre-specified HbA1c value

Patients without any available assessment at week 12 or week 24 will be considered as failures (non-responders) in the analysis.

Handling of missing data in the calculation of average pre-breakfast SMPG

At least 3 pre-breakfast SMPG values in the last 7 days are required to be taken into account in the statistical analyses (including descriptive analyses at each time-point).

Only fasting SMPG will be analysed.

Handling of missing data in the calculation of SMPG variables (4 points and 8 points profiles)

At least 5 measurements from the 8 points profile are required for analyzing the profile by time-point, the 24-hour mean SMPG and the corresponding variability.

At least 3 measurements from the 4 points profile are required for analyzing the profile by time-point.

Handling of missing data in the calculation of daily basal insulin dose

At each visit, the average daily basal insulin doses will be calculated as the average of the daily basal insulin doses available in the week before the visit. No minimum number of available doses will be required.

If the body weight measurement is missing at a given visit, the last available measurement from previous visit is used

In case of any missed doses, corresponding days should not be taken into account in the determination of the average daily insulin doses. In case of premature discontinuation or use of rescue medication, the average daily dose taken into consideration for a patient is the one measured the week before such event.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of adverse events/hypoglycemia with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events/hypoglycemia when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category “normal/missing at baseline.”

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Handling hypoglycemia with missing or partial time

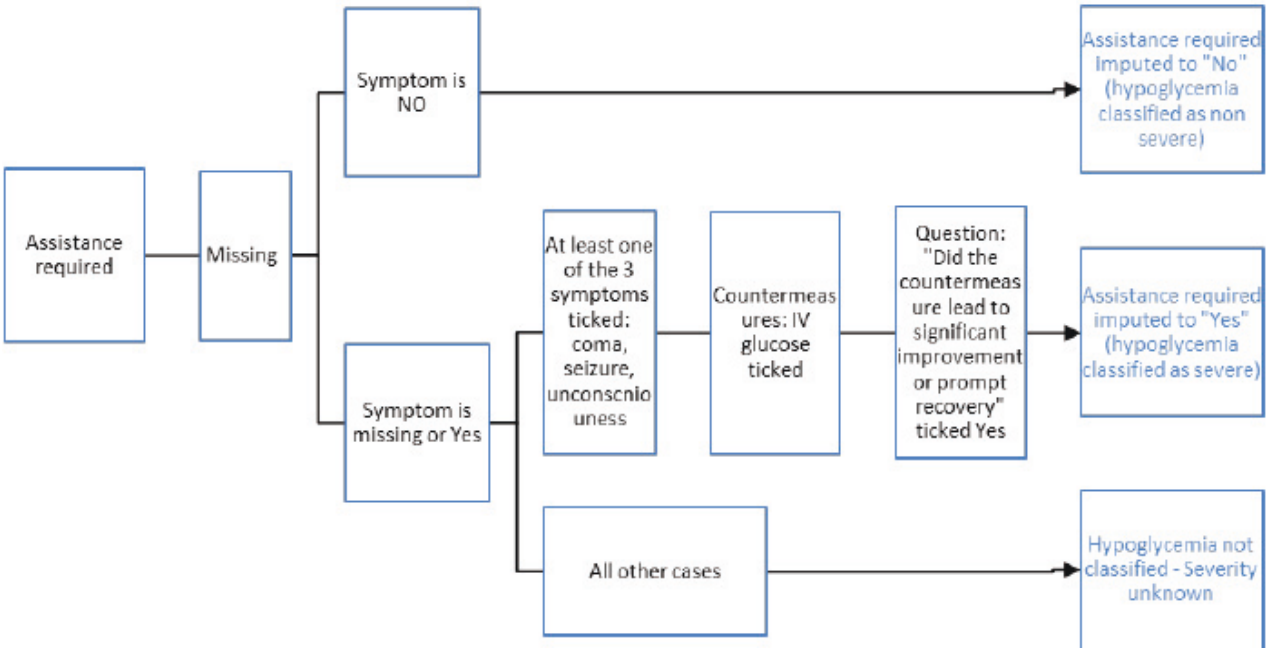
No imputation for missing or partial time of hypoglycemia will be done.

However:

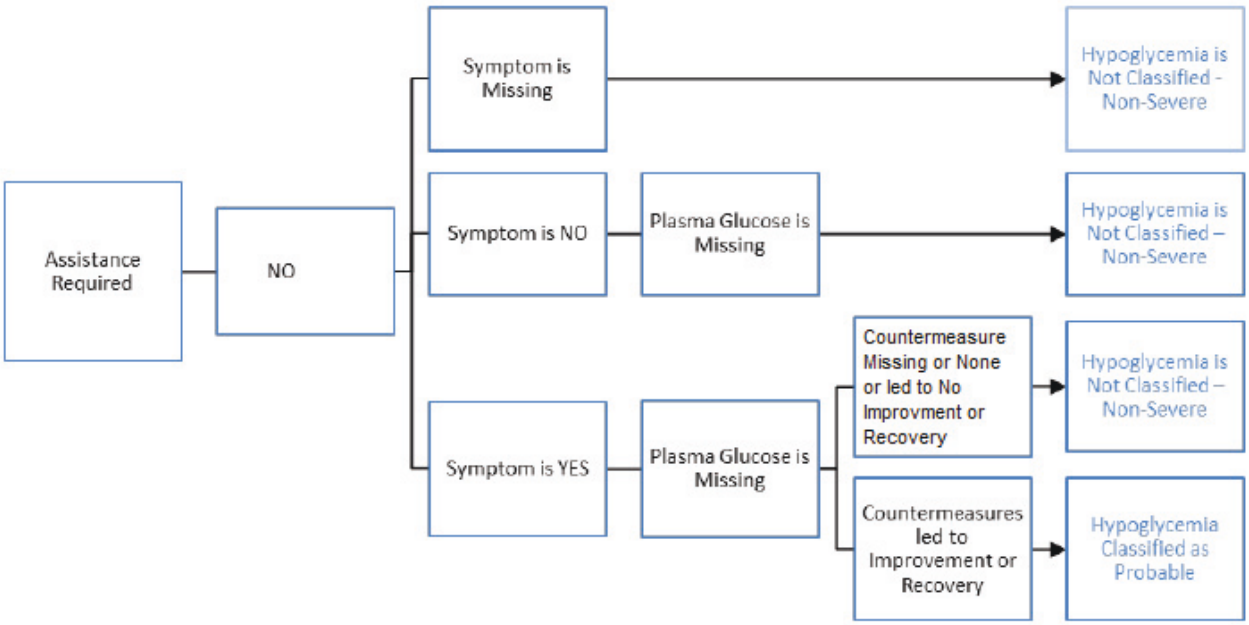
- if the minutes are missing and the hours comprised between 00 and 05, the event will be considered as nocturnal,
- if hours are missing and the patient was awaken during nocturnal, the event will be considered as nocturnal (defined by clock time).

Handling of hypoglycemia event classification when some classification items are missing

In case of information missing on the item 'Assistance required', the following algorithm was applied:



In case of 'assistance required' equal to 'No' and information missing on one of the items 'Associated with clinical symptoms', 'Plasma glucose' or 'Countermeasures', the following algorithm was applied:



As a conclusion, for cases where hypoglycemia could not be fully classified, as described above, two categories will therefore be created:

- hypoglycemia classified as 'Non classified Hypoglycemia (severity unknown) if the variable 'assistance required' is equal to 'missing'
- hypoglycemia classified as Non classified Hypoglycemia (non-severe) if the variable 'assistance required' is equal to 'No'.

2.5.4 Windows for time points

The following process will be applied for visit re-allocation. Re-allocated visits will be used in all statistical analyses (descriptive statistics, graphs, and statistical models).

No re-allocation will be performed for nominal visits already provided in the clinical database (Visit 1 to Visit 21), and for unscheduled assessments.

End of treatment visit

If a patient discontinues the treatment prematurely, end of treatment assessments will be re-allocated to the next scheduled on-site visit for the patient using the time windows given in Table 4. The next scheduled on-site visit for each patient will be determined as the next on-site visit that should be performed as per protocol, following the last visit actually performed by the patient before end of treatment visit.

For a given parameter, the value will not be re-allocated in the following cases:

- If the parameter is not planned to be collected at the re-allocation visit.
- If a value is already available for the parameter at the re-allocation visit. (ie, If a value (post EOT) is recorded for the same visit, it will be used instead of the reallocated one).

Table 4 - Reallocation time windows definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
HbA1c and FPG		
Week 8 (Visit 10)	57	43 to 70
Week 12 (Visit 12)	85	71 to 126
Week 24 (Visit 20)	169	127 to 182
Vital signs		
Week 2 (Visit 4)	15	7 to 21
Week 4 (Visit 6)	29	22 to 42
Week 8 (Visit 10)	57	43 to 70
Week 12 (Visit 12)	85	71 to 98
Week 16 (Visit 16)	113	99 to 126
Week 20 (Visit 18)	141	127 to 154
Week 24 (Visit 20)	169	155 to 182
8-point SMPG		
Week 12 (Visit 12)	85	43 to 126
Week 24 (Visit 20)	169	127 to 182
4-point SMPG		
Week 4 (Visit 6)	29	15 to 42
Week 8 (Visit 10)	57	43 to 70
Week 12 (Visit 12)	85	71 to 126
Week 24 (Visit 20)	169	127 to 182
HABS, DTSQs and DTSQc		
Week 12 (Visit 12)	85	43 to 126
Week 24 (Visit 20)	169	127 to 182

Study days are calculated from the day of first IMP, the day of first IMP injection being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

This process will be used to retrieve all assessments (including efficacy and safety) performed at the end of treatment visit.

Pre-rescue visit

If a patient takes rescue therapy, pre-rescue (visit 80) assessments will be re-allocated to the next scheduled on-site visit for the patient using the time windows given in Table 4. The next scheduled on-site visit for each patient will be determined as the next on-site visit that should be performed as per protocol, following the last visit actually performed by the patient before pre-rescue visit (visit 80).

For a given parameter, the value will not be re-allocated in the following cases:

- If the parameter is not planned to be collected at the re-allocation visit.
- If a value is already available for the parameter at the re-allocation visit. (ie. If a value (post rescue visit) is recorded for the same visit, it will be used instead of the reallocated one).

This process will be used to retrieve all assessments (including efficacy and safety) performed at the pre-rescue visit.

Last on-treatment value for vital signs

The last on-treatment value is the final measurement assessed during the on-treatment period, regardless of the introduction of rescue therapy, including measurements at unscheduled visits. A detailed definition of the on-treatment period is provided in Section 2.1.4.

2.5.5 Unscheduled visits

The determination of baselines and values at endpoints for efficacy variables is based on all measurements from both scheduled and unscheduled visits (measurements from the central laboratory only), as mentioned in Section 2.5.4. The determination of the last on-treatment value for safety parameters is also based on all assessments from both scheduled and unscheduled visits.

Measurements from the unscheduled visits are also considered for PCSA summary of safety parameters.

Unscheduled visit measurements are not included in the by-visit summaries.

2.5.6 Pooling of centers for statistical analyses

No pooling centers is planned for statistical analyses. Center and country will not be included in the statistical analysis.

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

No interim analysis will be performed during the study.

4 DATABASE LOCK

The database is planned to be locked at approximatively 7 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

6 REFERENCES

1. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.

2. Bradley C. The Diabetes Treatment Satisfaction Questionnaire: (DTSQ). In: Bradley C, editor. Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in DiabetesResearch and Practice. Chur (Switzerland): Harwood Academic Publishers;1994:111-32.

3. Bradley C, Plowright R, Stewart J, Valentine J, Witthaus E. The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) evaluated in insulin glargine trials shows greater responsiveness to improvements than the original DTSQ. Health Qual Life Outcomes. 2007;5:57.

4. Polonsky WH, Fisher L, Hessler D, Edelman SV. Identifying the worries and concerns about hypoglycemia in adults with type 2 diabetes. J Diabetes Complications. 2015;29(8):1171-6.

5. Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012; 367(14):1355-60.