STATISTICAL ANALYSIS PLAN

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

STUDY NUMBER: LPS14587

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	American Diabetes Association
AE:	adverse event
ALP:	alkaline phosphatase
ALT:	alanine transaminase
AM:	before midday
AST:	aspartate aminotransferase
ATC:	Anatomical Therapeutic Chemical
AUC:	area under the curve
BG:	blood glucose
BID:	twice per day
BMI:	body mass index
CGM:	Continuous Glucose Monitoring
CI:	confidence interval
CONGA:	continuous overall net glycemic action
CRF:	case report form
CV:	coefficient of variation
DBP:	diastolic blood pressure
DT:	distance traveled
FPG:	fasting plasma glucose
GFR:	glomerular filtration rate
HbA1c:	glycosylated hemoglobin
HLGT:	high group level term
HLT:	high level term
IMP:	investigational medicinal product
IVRS/IWRS:	interactive voice response system/interactive web response system
K-M:	Kaplan-Meier
LLT:	lower level term
MAGE:	mean amplitude of glycemic excursions
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified Intent-to-Treat
MMRM:	mixed-effect model with repeated measures
NIMP:	Non Investigation Medical Product
PCSA:	potentially clinically significant abnormality
PM:	after midday
PT:	preferred term
QD:	daily
SBP:	Systolic blood pressure
SD:	Standard deviation
SMPG:	self-measured plasma glucose
SOC:	system organ class

TEAE:	treatment-emergent adverse event
ULN:	Upper Limit of Normal
WHO-DD:	World Health Organization - Drug Dictionary
WOCBP:	women of childbearing potential

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multicenter, randomized, active-controlled, parallel group, 16-week open-label study. The study consists of an up to 4-week screening and Continuous Glucose Monitoring (CGM) training period and a 16-week treatment period (simple titration versus carbohydrate counting).

Patients satisfying the inclusion/exclusion criteria and CGM requirements are randomized 1:1 to morning injection of either Toujeo or Lantus. The randomization is stratified by baseline HbA1c (<8%, ≥8%), frequency of Lantus insulin injections at screening BID vs QD, current CGM use (yes/no) and mealtime insulin titration algorithm.

Approximately 616 patients are randomized, aiming for approximately 524 patients with evaluable data.

1.2 OBJECTIVES

1.2.1 Primary objectives

To demonstrate that morning injection of Toujeo compared to Lantus will provide better glycemic control evaluated by CGM in adult patients with type 1 diabetes mellitus.

1.2.2 Secondary objectives

To demonstrate that treatment with Toujeo compared to Lantus will provide

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

1.3 DETERMINATION OF SAMPLE SIZE

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

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

With the assumption of approximately 15% drop out rate, approximately 308 patients per treatment arm will provide at least 262 evaluable patients per treatment arm for the study.

Calculations were made using nQuery Advisor v6.01.

1.4 STUDY PLAN

The following study flow chart and figure describes the design of the study:

STUDY FLOW CHART

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

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

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

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

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

c Heart rate and blood pressure (sitting position)

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

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

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

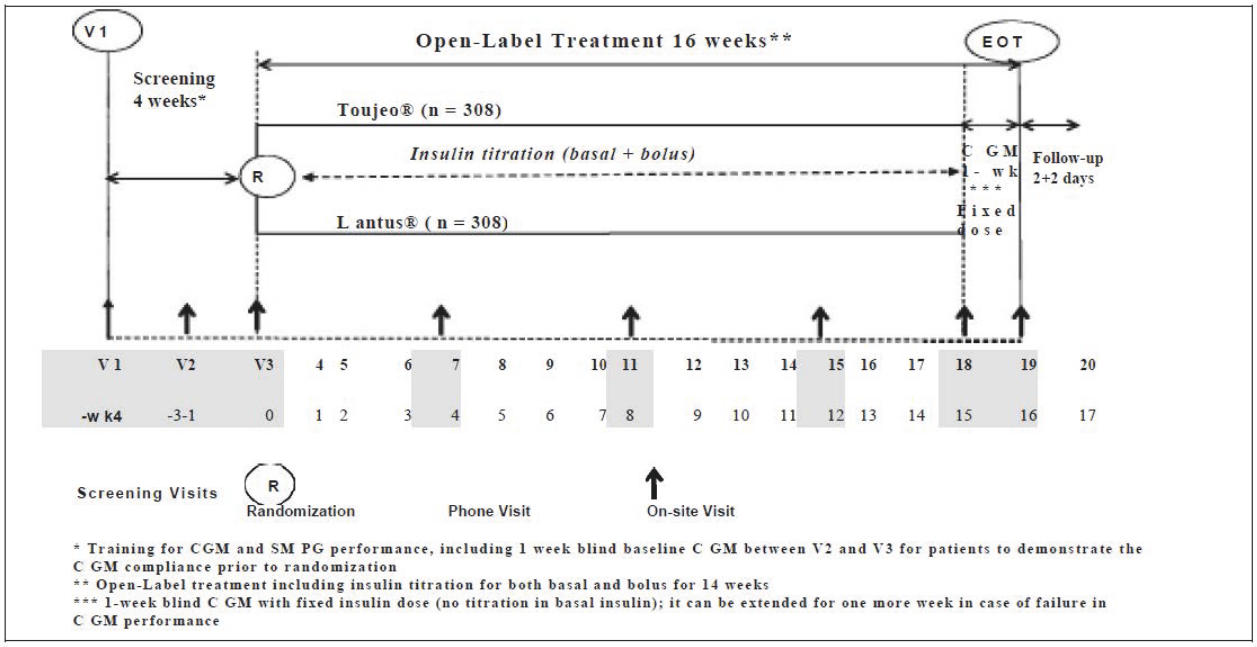
f Only for patients without documented test results to assess the relevant exclusions

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

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

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

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



LPS14587 is a multicenter, randomized, active-controlled, parallel group, 16-week open-label study. The study is a post-marketing Phase 4 trial which recruits outpatients with type 1 diabetes mellitus who have been on basal plus mealtime insulin regimen for at least one year and currently taking Lantus plus rapid-acting insulin analogs to manage their diabetes.

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

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

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

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

During the screening and baseline training period, patients wear a blinded CGM device for 7 consecutive days to generate a minimum of 4 days of usable CGM data to be eligible for

randomization. Patients satisfying the inclusion/exclusion criteria and CGM requirements are randomized 1:1 to morning injection of either Toujeo or Lantus. The randomization is stratified by baseline HbA1c (<8%, ≥8%), frequency of Lantus insulin injections at screening BID vs QD, current CGM use (yes/no) and mealtime insulin titration algorithm.

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

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

During the entire study starting after screening, patients will perform Self-Monitoring of Plasma Glucose (SMPG). SMPG readings are used to guide insulin dose-titration for optimal glycemic control and the SMPG profiles will be collected for study analyses.

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

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

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Additional secondary endpoint CGM parameters are added to assess glucose variability and some clarifications of the definition of CGM parameters are included in the statistical analysis plan.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Three statistical modifications were made in the statistical analysis plan.

1) Per protocol, during Week 15, patients will wear a blinded CGM device for 7 consecutive days to generate a minimum 4 days of useable CGM data. If a patient fails the first attempt for any reason, he/she will be retrained for CGM conduct and complete another course of blinded CGM in Week 16. If the patients fails the first week of CGM, only the second week CGM data will be used for data analysis and determine whether there are sufficient data to derive CGM variables. A statistical modification was made that if the second week CGM data are not sufficient per steps 1-6 above either and two weeks pooled together can generate a minimum 4 days of usable CGM data, then CGM data from both weeks will be pooled together to derive CGM variables.

2) An additional secondary endpoint, the mean change of each participant's glucose level during the last four hours of CGM data collection prior to next day's basal insulin injection, was added.

3) If there are more than hypoglycemia events within 30 minutes interval, the one with the lowest glucose level will be used.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

Baseline CGM measurements will start at Visit 2 and stop at randomization visit (Visit 3).

The baseline value for other efficacy and safety parameters is defined as the last available value before randomization visit (Visit 3).

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

Demographic characteristics

- Age (years),
- Age group (<65 and ≥65 years of age)
- Gender (Male, Female),
- Race (Caucasian/white, Black, Asian/Oriental, other),
- Ethnicity (Hispanic, non-Hispanic)
- Randomization strata of HbA1c obtained at the screening visit (<8.0% vs ≥8.0%), Frequency of Lantus injection at screening (BID vs QD), Lantus injection at screening (AM vs PM), current CGM use (yes/no) and mealtime insulin titration algorithm (carbohydrate counting versus simple titration).

Medical or surgical history

All medical/surgical history information, pre-listed or not in the 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

- Age at diagnosis of diabetes (years),
- Diabetes duration (years),

Specific disease history includes:

- Mealtime/bolus insulin at randomization (insulin glulisine, insulin lispro, and insulin aspart).
- Diabetic complications (including microvascular and neuropathic complications)
  - Diabetic retinopathy (yes/no/unknown),
  - Diabetic sensory or motor neuropathy (yes/no/unknown),
  - Diabetic nephropathy (yes/no/unknown).

2.1.2 Prior or concomitant medications

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 before screening 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 + 1 days. A given medication can be classified both as a prior medication and as a concomitant medication.
- Post-treatment medications are those the patient took in the period running from the last injection of IMP + 2 days (or 1 day for anti-diabetic therapies) to the end of the study.

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

During the study following medications are prohibited.

- Any antidiabetic agents other than the study medications mentioned above, including oral or injectable antihyperglycemic agents, other type of basal insulin (eg, NPH, Detemir, premixed insulin), and human regular insulin,
- Insulin pump therapy is not allowed during the course of the study,

- Initiation of any weight loss drugs is not allowed; previous treatment with weight loss drugs can be continued and doses must remain stable throughout the study,

- Systemic glucocorticoids for more than 10 consecutive days (topical or inhaled applications are allowed),

- Medications containing acetaminophen/paracetamol during the period of CGM performance as these medications can interact with the glucose sensor of the CGM device.

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

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

2.1.3 Efficacy endpoints

The baseline value for efficacy parameters is defined as the last available value before the first injection of IMP.

Baseline CGM measurements will start at Visit 2 and stop at randomization visit (Visit 3).

Observation period for efficacy endpoints

- The on-treatment period for efficacy variables is defined as the time from the first dose of IMP up to:

  - Seven (7) days after the last dose of IMP for HbA1c,

  - One (1) day after the last dose of IMP for hypoglycemia,

  - One (1) day after the last dose of IMP for FPG, SMPG and CGM,

  - Zero (0) day after the last dose of IMP for insulin glargine dose.

- The randomized period for efficacy variables is defined from the first dose of IMP up to Week 16 (visit 19).

All efficacy parameters will be performed on on-treatment period and randomized period.

All CGM derived variables will be subject to the following criteria.

1. CGM data are blinded to both the patients and investigators.

2. During the CGM performing week, the IMP insulin (Toujeo or Lantus) dose is fixed without a change, while the mealtime insulin dose can still be adjusted appropriately.

3. A complete 24-hour CGM profile includes 288 data points given that CGM reading is recorded every 5 minutes.

4. The start and end time of a 24-hour CGM profile is defined as midnight. i.e. each CGM profile begins at midnight (hour 0) and ends at midnight (hour 24 = hour 0). Partial CGM data points prior to the first midnight and after the last midnight from the visit will not be used in the CGM parameter calculation as the partial CGM profile may introduce additional variabilities to the data.

5. Useable CGM data for a day/a 24-hour CGM profile are defined as at least 85% time of records (245 data points) without a gap (missing data) lasting for ≥ 2 hours per 24 hours. At least 4 days of qualified 24-hour CGM records for each patient will be used for efficacy analyses. If the partial CGM data described in previously have at least 85% of a full CGM profile or 245 data points, the partial CGM profile will be used to calculate CGM parameters.

6. In cases that there are more than 288 data points or more than one data point per 5 minutes, usually due to recalibration or switching CGM devices, it will be reviewed and treated case by case. Usually averaging the data points every 5 minutes will be performed so that there is only one data point per 5 minutes.

7. Per protocol, during Week 15, patients will wear a blinded CGM device for 7 consecutive days to generate minimum 4 days of useable CGM data. If a patient fails the first attempt for any reason, he/she will be retrained for CGM conduct and complete another course of blinded CGM in Week 16. If the patients fails the first week of CGM, only the second week CGM data will be used for data analysis and determine whether there are sufficient data to derive CGM variables per steps 1-6 above. If the second week of CGM data are not sufficient per steps 1-6 above either, CGM data from the first week and the second week will be pooled together to repeat steps 1-6.

8. If a patient prematurely withdraws from the study before Week 15 (visit 18) the CGM data will be missing for the individual patient and the patient will be excluded from the primary efficacy analyses.

9. For all CGM parameters except the total and between day coefficient of variations (CV%) and standard deviations and area under the curve of glucose concentrations, a CGM parameter will be first calculated based on each 24-hour CGM profile from the visit, the final values of the CGM parameters for the visit will be based on the average of parameter values taken on each CGM profile from each CGM visit.

2.1.3.1 Primary efficacy endpoint(s)

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

The percentage of time glucose in target range 70-180mg/dL (3.9–10mmol/l) during weeks 15-16 (obtained from CGM) will be calculated based from the denominator of total time with valid data.

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

2.1.3.2 Secondary efficacy endpoint(s)

The main secondary efficacy endpoints include:

- Incidence and rate of nocturnal symptomatic hypoglycemia, defined as an event with typical symptoms of hypoglycemia accompanied by SMPG ≤70 mg/dL (3.9 mmol/L) that occurs between 00:00 and 05:59 hours,

- The mean change of each participant's glucose level during the last four hours of CGM data collection prior to next day's basal insulin injection (1) ,

- Percentage (%) of time glucose concentrations obtained by CGM within target range of 70-140 mg/dL (3.9–7.8 mmol/L) during the last 4 hours of CGM data collection prior to next day basal insulin injection,

- Total, within day and between day CV% in glucose values obtained from CGM.

Testing strategy of the six main secondary endpoints can be found in Section 2.4.4.3.

The other secondary efficacy endpoints include:

- Frequency and distribution (nocturnal or 24 hours) of all hypoglycemia events analyzed by hypoglycemia categories (severe, documented symptomatic, asymptomatic, probable and relative) as defined in the publication ADA Workgroup on Hypoglycemia, 2015 (see Appendix A),

- Additional CGM endpoints (data obtained at Week 16):

  - Percentage (%) of time glucose concentrations within the target range of 70-140 mg/dL (3.9–7.8 mmol/L), analyses on all-time (24 hours) CGM data.

  - Percentage (%) of time in hypoglycemia defined as percentage time with glucose concentrations <70 mg/dL (3.9 mmol/L) and <54 mg/dL (3 mmol/L), analyses on both all-time (24 hours) and nocturnal (00:00–05:59 h) CGM data

  - Percentage (%) of time in hypoglycemia defined as percentage time with glucose >140 mg/dL (7.8 mmol/L), >180 mg/dL (10 mmol/L) and > 250 mg/dL (13.9 mmol/l), analyses on both all-time (24 hours) and nocturnal (00:00–05:59 h) CGM data.

- Area under the curve (AUC) of glucose concentration <70 mg/dL (3.9 mmol/L), derived as the area below 70 mg/dL (3.9 mmol/L) and above the CGM profile (ie, the median curve), divided by the length of the evaluable assessment interval. The median curve will be obtained by superimposing the date-time-stamped glucose values collected by CGM into 24 nominal hourly baskets from which the point-wise median is calculated. For each patient, each evaluable day will have a glucose-time profile curve calculated. The AUC of glucose concentration <70 mg/dL (3.9 mmol/L) will be calculated for each patient day median curve. The mean AUC of glucose concentration <70 mg/dL (3.9 mmol/L) from each patient's all evaluable days will be used for further analysis.

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

Weighted mean 24-hour glucose, calculated by area under the median curve divided by the length of the evaluable assessment interval. The median curve will be derived as defined previously.

- other CGM glucose variability parameters include

(1) Total, within day and between day standard deviations (SDs).

$SD_{total} = \sqrt{\frac{\sum (x_i - \bar{x})^2}{k-1}}$, where x_i is individual glucose reading, $\bar{x}$ is the mean glucose readings from all evaluable CGM data points from all evaluable CGM profiles for the same visit. k is number of CGM data points.

$SD_{within} = \sqrt{\frac{\sum (x_i - \bar{x}_j)^2}{h-1}}$, where x_i is individual CGM data points within the CGM profile, $\bar{x}_j$ is the mean glucose readings from all CGM data points within the CGM profile. h is number of CGM data points. For each patient and visit, the within standard deviations from all CGM profiles will be averaged as the final value of the within standard deviation for the visit.

$SD_{between} = \sqrt{\frac{\sum (\bar{x}_j - \bar{x})^2}{m-1}}$, where m is the number of evaluable CGM profiles.

(2) Mean amplitude of glycemic excursions (MAGE), defined as mean glucose value by summing absolute rises and falls (local minima and maxima) of more than 1 SD. It includes only peak-to-nadir or nadir-to-peak excursions. $MAGE = \sum \frac{\lambda}{n}$ if $\lambda > SD$, where λ is the glucose increase or decrease (peak-to-nadir or nadir-to-peak excursions). n is the number of peak-to-nadir or nadir-to-peak excursions.

(3) Distance traveled (DT), defined as the sum of the absolute difference in glucose levels from the consecutive glucose measurements in the 24-hour CGM

profile. $DT = \frac{\sum | x_i - x_j |}{k*}$, where x_i and x_j are the two consecutive glucose measurements in the 24-hour CGM profile, and $k*$ is the number of the absolute differences in glucose levels.

(4) Total area under the curve (AUC), calculated by area under the median curve. The median curve will be derived as defined previously.

(5) Continuous overall net glycemic action (CONGA), defined as calculated as the SD of the summated differences between a current observation and an observation n hours previously. For this study, n=1, 2, 4 or CONGA-1, CONGA-2, CONGA-4 will be calculated. $\sqrt{\frac{\sum (D_i - \overline{D})^2}{k**-1}}$, where D_i is the difference between glucose reading at time t and t minus n hours ago from the 24-hour CGM profile and $\overline{D}$ is the mean difference. $k**$ is the number of D_i included in the 24 hour CGM profile.

- 7-point SMPG profiles (pre-prandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, and bedtime),
- Change from baseline to study endpoint in HbA1c,
- Change from baseline to treatment period endpoint in central lab FPG,

2.1.3.2.1 Hypoglycemia

2.1.3.2.1.1 Hypoglycemia classification

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 on-treatment period
- **Post-treatment hypoglycemia events** are events that occur during the post-treatment period

Hypoglycemia events will be categorized as defined in Appendix A. The glucose values used to classify hypoglycemia events are from the hypoglycemia e-CRF rather than the glucose values from CGM or central laboratory.

The incidence (proportion of patients with any hypoglycemia events) and the rate (number of events per patient year of exposure) will be assessed during each safety observation period for each hypoglycemia category.

In case of some classification items are missing (i.e. assistance required or not, presence of symptom, glycemic values, use of countermeasure) to determine hypoglycemia classification (see Section 2.5.3) the following categories will be presented.

- Not classified – non severe
- Not classified – severity unknown

2.1.4 Safety endpoints

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

The following safety parameters will be analyzed in this study:

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

Observation period

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

- The pre-treatment phase is defined as the time between when the patients give informed consent and time of the first IMP administration (excluded).
- **Treatment-emergent AEs (TEAEs)** are AEs that developed or worsened or became serious during the on-treatment period.
- The on-treatment phase is defined as the time from the first IMP administration (included) until 1 day after the last dose of IMP (until midnight of day after last IMP dosing day).
- The post-treatment phase is defined as the time after the on-treatment phase until the end of treatment.

2.1.4.1 Adverse events variables

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

The occurrence of AEs and SAEs is recorded from the time of signed informed consent until the end of the study. If an AE/SAE is ongoing and not resolved by the end of the study observation period (defined as the time from randomization until the end of the study) and leads to subsequent death of the patient, it will have to be reported.

2.1.4.2 Hypoglycemia

Hypoglycemia endpoints are described in Section 2.1.3.2.1.

2.1.4.3 Deaths

The death 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 on-study observation period
- 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 consist of blood analysis, including hematology, clinical chemistry, 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.

For purposes of determining patient eligibility, blood sampling for central laboratory assessments and urine sample collection will be performed at visit 1.

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

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

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

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

2.1.4.6 Electrocardiogram variables

Not applicable.

2.1.5 Pharmacokinetic variables

Not applicable.

2.1.6 Pharmacodynamic/genomics endpoints

Not applicable.

2.1.7 Quality-of-life endpoints

Not applicable.

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 patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients who have been allocated a treatment kit number as recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not.

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

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

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
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who did not complete the study treatment period as per protocol
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- 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 the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group.

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.

Additionally, the analysis populations for safety, efficacy will be summarized in a table by number of patients on the randomized population.

- Efficacy population: modified Intent-to-Treat (mITT) population, which will consist of all patients who are randomized and who have a post-baseline CGM assessment and enough data to calculate the primary endpoint, percent of time in range.
- Safety population

Treatment Persistence

- Kaplan–Meir plots (estimate) of cumulative incidence of permanent IMP discontinuation will be provided by treatment arm on the safety population.
- The hazard ratio of IMP permanent discontinuation of Toujeo arm over Lantus will be estimated along with its 95% CI on the safety population using a Cox regression model.

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).

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

- Treated but not randomized
- Randomized but not treated
- Randomized but not following the treatment arm as randomized

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

Randomization and drug allocation irregularities
Kit dispensation without IVRS 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.

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

2.3.1.1 Modified Intent–to-treat/Modified intent-to-treat population (mITT)

The efficacy analysis population will be the mITT population, which will consist of all patients who are randomized and who have a post-baseline CGM assessment and enough data to calculate the primary endpoint, percent of time in range of 70-180mg/dL (3.9–10mmol/L) during Week 16. Patients will be analyzed as-randomized.

2.3.2 Safety population

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

- Randomized patients for whom it is unclear whether they took the study medication will be considered as treated and included in the safety population.
- For patients receiving more than one study treatment during the trial, the treatment group allocation for as-treated analysis will be the treatment group in which he/she is treated for longer.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. 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. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

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

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.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (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 time for the same medication.

The table for 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, alphabetical order will be used.

The tables for concomitant and posttreatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence the overall incidence across treatment groups. In case of equal frequency regarding ATCs, alphabetical order will be used.

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 within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

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

Insulin dose (total, basal, mealtime/bolus, ratio of basal to bolus insulin dose) will be calculated.

Baseline and end of treatment IMP doses are the total daily IMP dose taken on the day of randomization and the total daily IMP dose taken at the end of the study. See Section 2.5.3 for baseline and end of treatment IMP dose calculation when the dose on randomization or end of treatment is missing.

Baseline and end of treatment meal time insulin doses are the average daily dose 3 days prior to randomization and the average daily dose 3 days prior to the last administration of IMP.

Insulin dose (total daily dose (units, units/kg), basal, mealtime/bolus, ratio of basal to bolus insulin dose) will be descriptively summarized for absolute values and change from baseline to the end of treatment. Mean insulin doses will also be plotted over time.

2.4.3.2 Compliance

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

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

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

The percentage of time glucose in target range 70-180mg/dL (3.9–10mmol/l) during week 16 (obtained from CGM) will be calculated based from the denominator of total time with valid data. The criteria to evaluate baseline and Week 16 CGM data are in Section 2.1.3.

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

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

Differences between treatment groups will be assessed using a generalized linear model with identity link, adjusting for key baseline characteristics (duration of diabetes, baseline BMI, age and baseline value) and randomization strata if model permits. If model does not converge, for example due to over 90% patients fall into the carbohydrate counting, the specific factors which cause non convergence may be dropped from the model. Adjusted mean estimates for each treatment group with standard errors, the adjusted estimate of treatment mean difference with standard error and a 95 % confidence interval for the treatment mean difference will be provided. The statistical test will be for superiority of Toujeo over Lantus, two-sided and at a 5% significance level.

2.4.4.2 Analyses of secondary efficacy endpoints

The main secondary efficacy endpoints.

The seven main secondary efficacy endpoints will be analyzed as below and tested sequentially after the primary endpoint. Testing strategy is described in 2.4.4.3

The incidence (proportion of patients with any nocturnal symptomatic hypoglycemia events) will be analyzed using logistic regression, adjusting for randomization strata and other baseline characteristics (duration of diabetes, baseline BMI and age) if the model permits.

The risk ratio (RR) of hypoglycemia of Toujeo versus Lantus will be assessed by a log-binomial regression model adjusting for randomization strata and other baseline characteristics (duration of diabetes, baseline BMI and age) if the model permits.

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

The mean change of each participant's glucose level during the last four hours of CGM data collection prior to next day basal insulin injection comparing Toujeo versus Lantus will be analyzed using a mixed model, in which treatment arm is a fixed categorical effect and patient is a random effect, adjusting for randomization strata and other baseline characteristics (duration of diabetes, baseline BMI and age) if the model permits. If a patient has more than 7 evaluable days of CGM data, only the first 7 days closest to Week 15 will be included.

The percentage of time glucose concentrations obtained by CGM within the target range of 70-140 mg/dL (3.9-7.8 mmol/L) during the last 4 hours of CGM data prior to the next day basal insulin injection will be summarized and analyzed by the same model as the primary endpoint.

Total, within day and between day standard deviation (SD) will also be summarized and analyzed by the same model as the primary efficacy endpoint.

Other endpoints

The total, within day and between day CV% and SD will be summarized at baseline and study endpoint by treatment group using mean, median, standard deviation, minimum and maximum, and will be analyzed as for the primary endpoint.

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

The percentage of time plasma glucose in target range 70-140 mg/dL (3.9–7.8 mmol/L), the percentage of time plasma glucose <70 mg/dL (3.9 mmol/L), <54 mg/dL (3 mmol/L), the percentage of time glucose >140 mg/dL (7.8 mmol/L), >180 mg/dL (10 mmol/L) and > 250 mg/dL (13.9 mmol/l) will be calculated and summarized and analyzed as for the primary endpoint. For these endpoints, the time period of observation will be all evaluable time (24 hours) and nocturnal, where nocturnal is defined as the period between 00:00-05:59 within the evaluable assessment interval.

All other continuous CGM endpoints including the glucose variability parameters (MAGE, DT, AUC, CONGA-1, CONGA-2, CONGA-4) will be summarized, and will be analyzed using the same model as described for the primary endpoint.

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

Summary statistics will also be presented for the absolute values and the change from baseline in HbA1c and central lab FPG to Week 8, Week 16 and last on-treatment value (study endpoint). The change from baseline to study endpoint will be analyzed using a mixed-effect model with repeated

measures (MMRM) approach under the missing at random framework, using an adequate contrast at endpoint. The model will include fixed categorical effects of treatment arm, visit, treatment-by-visit interaction, randomization strata, and baseline HbA1c as covariate as well as baseline HbA1c-by-visit interaction.

Median, the first and the third quartiles and 10% and 90% percentiles of the curves, which are used to calculate the primary endpoint and secondary CGM endpoints, will be plotted for each treatment group.

2.4.4.3 Multiplicity issues

Results of the secondary analyses are considered as informative only if the primary analysis is positive, and will be examined in a hierarchical step-down manner. The primary efficacy endpoint, the percentage of time glucose in target range 70-180mg/dL (3.9–10 mmol/l) during Week 16, will be tested first, followed by (1) incidence of nocturnal symptomatic hypoglycemia, (2) rate of nocturnal symptomatic hypoglycemia, (3) mean change of each participant's glucose level during the last four hours of CGM (4) percentage (%) of time glucose concentrations obtained by CGM within target range of 70-140 mg/dL (3.9–7.8 mmol/L) during the last 4 hours of CGM data collection prior to next day basal insulin injection, (5) total CV%, (6) within day CV% and (7) between day CV% . Each test was planned to be performed at 5% significance level. Inferential conclusions about these successive efficacy endpoints will require statistical significance of the previous one.

For other secondary and exploratory endpoints, nominal p-values will be presented for information only.

2.4.5 Analyses of safety data

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment and posttreatment 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 posttreatment. 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 posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and posttreatment). 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.

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

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

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

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

2.4.5.2 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 nonrandomized patients or randomized but not treated patients

2.4.5.3 Analyses of hypoglycemia variables

Hypoglycemia analyses described in Section 2.4.4.2 will be repeated based on Safety Population.

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

The incidence (proportion of patients with any nocturnal symptomatic hypoglycemia events) will be analyzed using logistic regression, adjusting for randomization strata and other baseline characteristics (duration of diabetes, baseline BMI and age) if the model permits.

The risk ratio (RR) of hypoglycemia of Toujeo versus Lantus will be assessed by a log-binomial regression model adjusting for randomization strata and other baseline characteristics (duration of diabetes, baseline BMI and age) if the model permits.

2.4.5.4 Analyses of electrocardiogram variables

Not applicable.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

Not applicable.

2.4.7 Analyses of quality of life/health economics variables

Not applicable.

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 open-label IMP, denoted as Day 1.

Demographic formulas

Body Mass Index (kg/m^2)= (Weight in kg) / $(\text{Height in meters})^2$

Disease characteristics formulas

Diabetes duration of (years) will be calculated as follows
= (Date of informed consent – Date of diagnosis of diabetes + 1)/365.25

Age at diagnosis of diabetes (years) will be calculated as follows
= (Date [MM-YYYY] of diagnosis of diabetes – date [MM-YYYY] of birth +1) /365.25.

In case of unavailable date of birth, only the year of the date of diabetes diagnosis and the year of the date of birth (retrieve using the age recorded at screening) will be considered in the age at diagnosis of diabetes calculation.

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.

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 CGM measurements outside detection range

CGM blood glucose values below the lower limit and above upper limit of detection range will be set to the lower and upper limits of detection, respectively, for the CGM parameter derivation.

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 missing baseline and end of treatment IMP doses

For baseline and end of treatment IMP dose calculations, if the dose on the date of randomization or the dose at the end of treatment is not available, the last available dose within 2 days prior to randomization and the last available dose within 2 days prior to the end of the treatment will be used.

Handling of missing IMP injection time for the purpose of CGM parameter calculation

For the calculation of secondary efficacy end point, percentage time glucose concentrations obtained by CGM within target range of 70-140 mg/dL (3.9–7.8 mmol/L) during the last 4 hours of CGM data collection prior to next day basal insulin injection, if the injection time of the IMP is missing, the injection time from the prior day will be used as it is assumed that IMP should be injected at the same time in the morning.

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 posttreatment medication.

Handling partial date of birth:

For calculation age, missing birth day is assumed as the 15 of the month. If month is missing, the age will be calculated as Year of date of consent- Year of birth.

Handling of partial date of diagnosis of Type 1 diabetes

Partial date of diagnosis of Type 1 diabetes will be imputed to calculate the duration of diabetes.

In order to calculate:

- Duration of diabetes (year)
- Age at diagnosis of diabetes (year)

If only day is missing, only month and year will be used. If month is missing, only year will be used in calculation.

Handling of potentially clinically significant abnormalities

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

Handling of missing hypoglycemia data

To determine nocturnal symptomatic hypoglycemia, if the time of hypoglycemia is not captured, the time of BG collected from the hypoglycemia e-CRF will be used. If more than one hypoglycemia event is reported, the earliest time stamp and lowest BG level, requiring assistance will be used to determine the hypoglycemia event type.

Handling of more than one hypoglycemic events within 30 minutes interval

If there are more than hypoglycemia events within 30 minutes interval, the one with the lowest glucose level will be used.

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 20), 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. 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.

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

2.5.5 Unscheduled visits

The determination of baselines and values at Weeks 15-16 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 of 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 is planned.

4 DATABASE LOCK

The database is planned to be locked approximately 4 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS Enterprise Guide version 5.1 or higher.

6 REFERENCES

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2. American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes, Diabetes Care. 2005; 28:1245-9.