NCT Number: NCT02735044

STATISTICAL ANALYSIS PLAN

6-Month, Multicenter, Randomized, Open-label, 2-Arm, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® Injected Once Daily in Children and Adolescents age 6 - 17 years with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period

HOE901-EFC13957

STATISTICIAN: [redacted]

BIOSTATISTICS PROJECT LEADER: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	american diabetes association
ADaM:	Analysis Data Model
AE:	adverse event
AIA:	anti-insulin antibodies
ALP:	alkaline phosphatase
ALT:	alanine aminotransferases
ANCOVA:	analysis of covariance
AST:	aspartate aminotranferases
ATC:	anatomic category class
BMI:	body mass index
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CSR:	clinical study report
e-CRF:	e-case report form
eGFR:	estimated glomerular filtration rate
EOT:	end of treatment
FDA:	Food and Drug Administration
GFR:	glomerular filtration rate
HbA1c:	Glycated hemoglobin A1c
HLGT:	high-level group term
HLT:	high-level term
IMP:	investigational medicinal product
ISPAD:	International Society for Pediatric and Adolescent Diabetes
ITT:	intent-to-treat
IVRS:	interactive voice response system
IWRS:	interactive web response system
KM:	Kaplan-Meier
MCMC:	Markov Chain Monte Carlo
MedDRA:	Medical Dictionary for Regulatory Activities
NIMP:	non-investigational medical product
PCSA:	potentially clinically significant abnormality
PK:	pharmacokinetics
PKDM:	pharmacokinetics, dynamics and metabolism
PT:	preferred term
ROW:	rest of the world
SAE:	serious adverse event
SAP:	statistical analysis plan
SAS:	statistical analysis system
SD:	standard deviation
SE:	standard error
SEM:	standard error of the mean

SMPG:	self-measured plasma glucose
SMQ:	standardized medDRA query
SOC:	system organ class
T1DM:	type 1 Diabetes Mellitus
TEAE:	treatment-emergent adverse event
TEAE:	treatment-emergent adverse event
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 an open-label, 1:1 randomized, active-controlled, 2-arm parallel-group, multicenter international, phase 3b study comparing HOE901-U300 versus Lantus in children and adolescents with T1DM. Patients will continue their fast-acting mealtime insulin analogue during the study.

Randomization will be stratified by age group (<12 years and ≥12 years) and by HbA1c (<8.5% and ≥8.5%) at screening. Inclusion in the study is configured to ensure at least 30% of participants in the age range below 12 years.

At the end of the screening period, eligible patients will be randomized to one of the two treatment groups: HOE901-U300 or Lantus.

Approximately 450 patients (225 patients per treatment group) will be randomized from approximately 109 sites.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the non-inferiority of a new formulation of insulin glargine (HOE901-U300) to Lantus in terms of change of HbA1c from baseline to endpoint (Month 6) in children and adolescents age 6-17 years with type 1 diabetes mellitus

1.2.2 Secondary objectives

- To compare HOE901-U300 and Lantus in terms of:
  - Percentage of patients reaching target HbA1c (<7.5%) at Month 6 overall and without any episode of severe and/or documented hypoglycemia during last 3 months of the main 6-month randomized period,
  - Change from baseline to endpoint (Month 6) in fasting plasma glucose (central laboratory),
  - Percent of patients reaching target FPG value (≤130 mg/dL [7.2 mmol/L]) at Month 6 overall and without any episode of severe and/or documented hypoglycemia during the last 3 months of the main 6-month randomized period,
  - Change in mean self-monitored plasma glucose (8-point SMPG profiles per time-point [pre-prandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, bedtime plasma glucose, nocturnal plasma glucose], 24-hour mean plasma glucose, variability of 24-hour mean plasma glucose) from baseline to Month 6.

- To assess the safety of HOE901-U300 including analysis of events of hypoglycemia, events of hyperglycemia with ketosis and development of anti-insulin-antibodies.
- To assess the extent of accumulation and metabolism of HOE901-U300 versus Lantus in this age group.

1.3 DETERMINATION OF SAMPLE SIZE

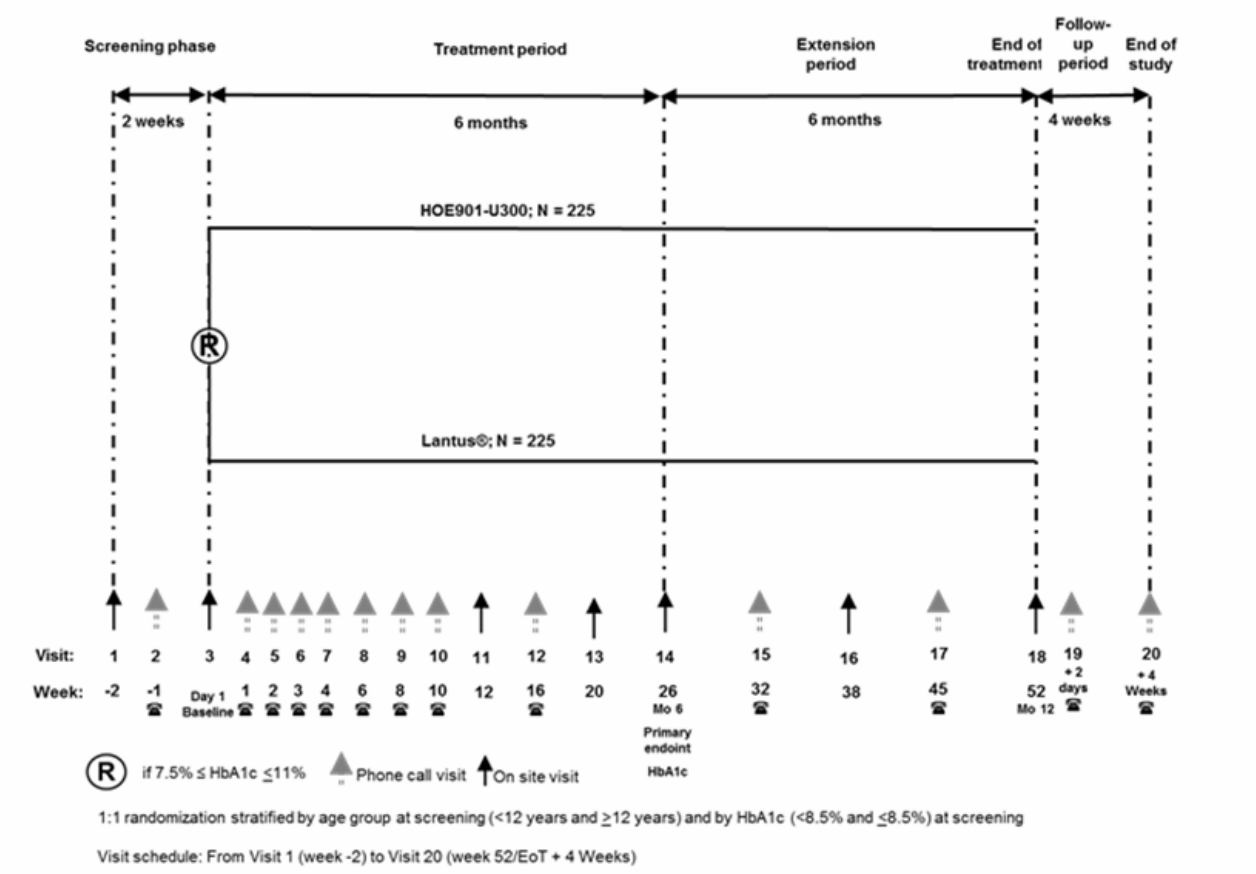
The sample size calculation is based on the primary efficacy variable of HbA1c change from baseline to Month 6/Week 26.

A sample size of 450 randomized patients (225 for HOE901-U300 and 225 for Lantus) will ensure that the upper bound of the two-sided 95% confidence interval (CI) for the adjusted mean difference between HOE901-U300 and Lantus would not exceed a non-inferiority margin of 0.3% with 92% power. This calculation assumes a common standard deviation (SD) of 0.95%, with a one-sided test at the 2.5% significant level and a true difference of zero in HbA1c between treatment groups.

Calculations were made using East® Software Version 6.3.

1.4 STUDY PLAN

The following figure describes the design of the study:



The study consists of:

- A 2-week screening period.
- A 6-month comparative efficacy and safety treatment period.
- A 6-month comparative safety extension period.
- A 4-week post-treatment follow up period.

In case of premature permanent discontinuation of study treatment, patients will be asked to continue attending study visits and undergo assessments according to the schedule until the planned end of study treatment (Month 12), including assessments normally scheduled for the 4-week post-treatment follow up period. As a minimum, visit at Week 26/Visit 14 (assessments of primary and secondary efficacy endpoints) should be conducted. For safety considerations, patients/parents who withdraw consent for further participation in the study, at the minimum should be contacted 2 days after last intake of the IMP.

In total the study duration per patient will be approximately 58 weeks (2 weeks of screening + 52 weeks of treatment + 4 weeks of post-treatment follow up).

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes made after study start (after the first patient was enrolled).

There are no planned interim analyses.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	23-Aug-2016	*FDA recommendation*	*Mixed-effect model with repeated measures (MMRM) for the analysis of the primary and secondary endpoints is replaced by a multiple imputation approach where missing data from subjects who do not adhere to therapy are represented by the data from those subjects on the same arm that also did not adhere to therapy but had the measurement for the primary endpoint. Change to statistical methodology in primary and secondary endpoint analyses sections*
2	23-Aug-2016	*Correction of software used for sample size calculation*	*nQuery Advisor® Software Version 7.0. replaced by East® Software Version 6.3.*
2	23-Aug-2016	*Clarification of baseline definition for efficacy variables*	*Definition of baseline for efficacy variables is defined in the SAP as the last available value obtained up to the date and time of randomization or up to the time of first injection of IMP if occurred at the day of randomization*
2	23-Aug-2016	*BfArM requests*	*The objective of non-inferiority testing is clearly and more prominently presented in section 1.2.1 Primary objectives.* *Data from the extension period relative to efficacy will be analyzed and the corresponding endpoints are clearly added in the section 2.1.3.2 Secondary efficacy endpoints*
2	23-Aug-2016	*Modifications for clarification*	*The key sensitivity analysis in the protocol is renamed supportive analysis in the SAP and the text is updated for clarification*
2	23-Aug-2016	*Deletion of penalized multiple imputation analysis as it is included in the tipping-point analysis for the sensitivity analysis of the primary efficacy analysis*	*The sensitivity analysis, penalized multiple imputation analysis, is deleted*

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	23-Aug-2016	*Modification for consistency with the primary efficacy analysis*	*Imputation models in the tipping-point analysis include change from baseline HbA1c at post-baseline time points instead of HbA1c value for consistency with primary efficacy analysis*
2	23-Aug-2016	*Correction*	*PK population is updated as below: "*All patients randomized and treated patients who provided at least one PK measurement will be included in the PK population *"*
2	23-Aug-2016	*Correction for more relevant analyses*	*Analyses of hypoglycemia planned in the protocol on severe and/or documented symptomatic hypoglycemia are planned in the SAP on severe and/or documented hypoglycemia ("symptomatic" deleted)*

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable

2 STATISTICAL AND ANALYTICAL PROCEDURES

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

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined generally as the last available value obtained up to the date and time of randomization or up to the time of first injection of IMP if occurred at the day 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 and disease characteristics at baseline will be provided overall and by randomization stratum of age at screening (<12 years and ≥12years).

Demographic characteristics

Demographic characteristics at baseline

- Age (years).
- Randomization strata of age group (<12, ≥ 12 years of age).
- Randomization strata of screening HbA1c categories (<8.5; ≥8.5%).
- Gender (Male, Female).
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Japanese, Not reported, Unknown).
- Ethnicity (Hispanic, not Hispanic, Not reported, Unknown).
- Regions (North America, South/Latin America, Western Europe, Eastern Europe, Rest of the World (ROW)) / Countries.
- Body height (cm).
- Body weight (kg).
- Body Mass Index (kg/m²) percentile (1).
- BMI percentile categories: <5th percentile; 5th-<85th percentile; 85th-<95th percentile; ≥95th percentile.
- Tanner puberty stage evaluation (pre-pubertal, adolescent, adult).
- For girls, postmenarchal status (Yes/No).

- Estimated glomerular filtration rate (eGFR, using Schwartz formula (2, 3), mL/min/1.73m²),
- Estimated GFR categories (mL/min/1.73m2):
  - ≥90; [60 – 90[; [30 – 60[; <30.
  - <30; [30-60[; ≥60

Medical or surgical history

All medical/surgical history information (including allergies, diabetic ketoacidosis, diabetic complications, history of seizure/coma and/or hospitalization due to severe hypoglycemia), 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.

Disease characteristics at baseline

Diabetes history will include:

- Duration of diabetes (years).
- Category of duration of diabetes (<2; [2 - 5[; ≥5 years).
- Age (years) at onset of diabetes.
- Antibody (GAD2, Insulinoma-Associated Protein 2, Islet Cell 512 antibodies)) status at diagnosis (positive, negative).
- C-peptide at diagnosis (positive, negative).
- Previous basal insulin treatment:
  - Daily dose (U and U/kg) = median of previous basal insulin daily doses during the last 3 days prior to the first IMP (or prior to randomization for not treated patients),
  - Daily injection number (once daily, twice daily, more than twice daily),
  - Product, for last 3 month before visit 1 only, (insulin glargine, insulin detemir, NPH, other); daily dose and daily injection number will be provided by product too.
- Previous mealtime insulin treatment:
  - Daily dose (U and U/kg) = median of previous mealtime insulin daily doses during the last 3 days prior to the first IMP (or prior to randomization for not treated patients),
  - Product; daily dose will be provided by product too.
- Previous total insulin treatment:
  - Daily dose (U and U/kg): sum of previous basal plus mealtime, during the last 3 days prior to the first IMP (or prior to randomization for not treated patients).

- Previous anti-hyperglycemic treatment other than insulin within 3 months prior to first IMP:
  - Previous anti-hyperglycemic treatment by chemical class.
- History of acute and chronic diabetic complications will be collected via the standard medical history form.

Baseline efficacy data

The baseline value for efficacy variables is the last available value obtained up to the date and time of randomization or up to the time of first injection of IMP if occurred at the day of randomization.

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 2.5.3 for handling of missing data).

Insulin dose at baseline

- Basal insulin daily dose at baseline (U and U/kg) = intended dose reported in the e-CRF.
- Mealtime insulin daily dose at baseline (U and U/kg) = median of mealtime insulin daily doses of the 3 first days from the first IMP. The first mealtime insulin daily dose is identified by the start date reported on the visit 4 form for the IMP exposure in the e-CRF.
- Total insulin daily dose at baseline (U and U/kg) = intended dose of basal insulin plus median of mealtime insulin daily dose.

Smoking/alcohol habits

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

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 + 2 days (or 0 day for anti-diabetic therapies). 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 + 3 days (or 1 day for anti-diabetic therapies) to the end of the study.

Anti-diabetic medications will be identified by a pre-defined list of ATC codes provided in the ADaM metadata.

2.1.3 Efficacy endpoints

The baseline value for efficacy variables is the last available value obtained up to the date and time of randomization or up to the time of first injection of IMP if occurred at the day of randomization.

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

Observation period for efficacy endpoints

- The main 6-month randomized period for efficacy variables is defined as the time from randomization up to Month 6 (Visit 14) for randomized patients, regardless of study treatment discontinuation.
- The 12-month randomized period for efficacy variables is defined as the time from randomization date up to Month 12 (Visit 18) for randomized patients, regardless of study treatment discontinuation.
- The main 6-month on-treatment period for efficacy variables is defined as the time from the first dose of IMP up to Month 6 (visit 14) or, in case of premature treatment discontinuation before Month 6, up to:
  - 7 days after the last dose of IMP for HbA1c,
  - 2 days after the last dose of IMP for hypoglycemia,
  - 1 day after the last dose of IMP for FPG and SMPG value.
- The 12-month on-treatment period for efficacy variables is defined as the time from the first dose of IMP up to:
  - 7 days after the last dose of IMP for HbA1c,
  - 2 days after the last dose of IMP for hypoglycemia,
  - 1 day after the last dose of IMP for FPG and SMPG value.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy variable is the change in HbA1c from baseline to Week 26 which is defined as: HbA1c value at Week 26 – HbA1c value at baseline (%) in the ITT population, using all HbA1c values regardless of adherence to treatment (ITT estimand). Results for the primary efficacy variable will also be presented in mmol/mol.

2.1.3.2 Secondary efficacy endpoint(s)

All secondary endpoints are calculated on the main 6-month randomized period using the ITT population (ITT estimand).

- Percentage of patients with HbA1c values of <7.5% at Week 26.
- Percentage of patients with HbA1c values of <7.5% at Week 26 without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) hypoglycemia during the last 3 months of the main 6-month randomized period (from randomization date up to Month 6 (Visit 14), regardless of study treatment discontinuation).
- Change in FPG from baseline to Week 26 (central laboratory).
- Percentage of patients with fasting plasma glucose (FPG) ≤130 mg/dL (7.2 mmol/L) at Week 26.
- Percentage of patients with fasting plasma glucose (FPG) ≤130 mg/dL (7.2 mmol/L) at Week 26 without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) hypoglycemia during the last 3 months of the main 6-month randomized period.
- Change in 24-hour mean plasma glucose based on 8-point SMPG profiles from baseline to Week 26.
- Change in variability of 24-hour mean plasma glucose based on 8-point SMPG profiles from baseline to Week 26 (the variability being assessed by the mean of coefficient of variation calculated over the 8-point SMPG).
- Change in 8-point self-monitored plasma glucose (SMPG) profiles per time-point from baseline to Week 26 (pre-prandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, bedtime plasma glucose, nocturnal plasma glucose).

The change in average pre-breakfast SMPG from baseline to Week 26 will be analyzed as additional exploratory secondary efficacy endpoint.

For descriptive purpose, all secondary endpoints will be evaluated at end of the 12-month randomized period, ie, at Week 52. They will be also evaluated at intermediary timepoints (Week 12, Week 20, Week 38) when applicable.

2.1.4 Safety endpoints

The safety analysis will be based on hypoglycemia events, injection site reactions, hypersensitivity reactions, hyperglycemia with ketosis, adverse events and other safety information, such as clinical laboratory data, vital signs.

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

Observation period of safety endpoints

The observation period of safety data will be divided as follows:

- The pre-treatment period is defined as the time between the date of the informed consent and the first injection of IMP.
- The main 6-month TEAE period is defined as the time from the first injection of open label IMP up to Month 6/ Week 26 (visit 14) or up to 2 days after the last injection of IMP, whichever comes earlier.
- The 12-month TEAE period is defined as the time from the first injection of IMP up to 2 days after the last injection of IMP.
- The post-treatment period is defined as the time starting 3 days after last injection of IMP (after the TEAE period).

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 of special interest).

2.1.4.1 Hypoglycemia events

Hypoglycemia events will be categorized as follows using the criteria published by the ADA (4, 5) and ISPAD (6):

- Severe hypoglycemia

Severe hypoglycemia is defined as the child/adolescent having altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or glucose).

- Documented symptomatic hypoglycemia

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

- Asymptomatic hypoglycemia

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

- Probable symptomatic hypoglycemia

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

- Pseudo-hypoglycemia

Pseudo-hypoglycemia is an event during which the child/adolescent with diabetes reports any of the typical symptoms of hypoglycemia, but with a measured plasma glucose concentration greater than 70 mg/dL (3.9 mmol/L); symptoms are relieved with a countermeasure.

The composite category of severe and/or documented (≤70 mg/dL; 3.9 mmol/L) hypoglycemia will be presented too.

In addition to the threshold of ≤70 mg/dL (3.9 mmol/L), the following hypoglycemia categories will be also evaluated for the more stringent SMPG threshold of <54 mg/dL (3.0 mmol/L): documented symptomatic hypoglycemia; asymptomatic hypoglycemia; severe and/or documented hypoglycemia.

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

- Nocturnal hypoglycemia (defined by time of the day): any hypoglycemia that occurs between 00:00 and 05:59 a.m. hours, regardless whether patient was awake or woke up because of the event.
- Daytime hypoglycemia (defined by time of the day): any hypoglycemia that occurs between 6:00 a.m. to 23:59.
- Nocturnal hypoglycemia (defined by sleep status): any hypoglycemia waking the patient up from sleep after having gone to bed in the evening and before getting up in the morning (ie, before the morning determination of fasting pre-breakfast SMPG and before administration of insulin (IMP or NIMP).

Some analyses will be also performed by distribution by hour of the day (0:00-23:59).

Hypoglycemia episodes will be also analyzed according the following periods:

- For the 6-month CSR:
  - 6-month TEAE period,
    - From first injection of IMP to end of Week 8,
    - From start of Week 9 to Month 6.
- for the 12-month CSR:

- 12-month TEAE period.
- Post-treatment period (4-week follow-up).

Some analyses will be also performed by monthly rates.

All hypoglycemia events reported by the investigator as severe and/or reported as serious adverse events including those with seizure, loss of consciousness, coma and/or events treated with iv glucose or glucagon will be independently reviewed under blinded conditions by the External Endpoint Assessment Committee. The result of this external review of severe hypoglycemia classification will be analyzed separately.

2.1.4.2 Hyperglycemia with ketosis

Hyperglycemia with ketosis data will be analyzed according to the two definitions:

- Self-measured blood ketones ≥1.5 mmol/L.
- Self-measured plasma glucose ≥252 mg/dL (14 mmol/L) and self-measured blood ketones ≥1.5 mmol/L.

Ketosis/ ketoacidosis related adverse events will be identified using MedDRA searches listed in the ADaM metadata.

Hyperglycemia with ketosis analyses will be performed according the following periods:

- For the 6-month CSR:
  - 6-month TEAE period.
- For the 12-month CSR:
  - 12-month TEAE period,
  - Post-treatment period (4-week follow-up).

2.1.4.3 Adverse events variables

Adverse event observation period

- Pre-treatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of IMP.
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period.
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period.

All adverse events will be coded to a “Preferred Term” (PT) and “High Level Group Term”(HLGT), “High Level Term” (HLT) and primary “System Organ Class” (SOC) using the version of MedDRA currently in use by the sponsor at the time of database lock.

Injection site reaction adverse events and hypersensitivity reactions adverse events will be identified using MedDRA searches listed in the ADaM metadata.

Adverse events of special interest include:

- Symptomatic overdose (accidental or intentional) with IMP/NIMP (event suspected by the investigator or spontaneously notified by the patient/parent [not based on systematic drug accountability]).
- ALT increase (>=3 ULN or >2 times the baseline value).
- Pregnancy.

2.1.4.4 Deaths

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

- Death on-study: deaths occurring during 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.

2.1.4.5 Laboratory safety variables

The following laboratory safety variables will be analyzed:

- Hematology:
  - **Red blood cells and platelets** erythrocytes, hemoglobin, hematocrit, leukocytes and platelets,
  - **White blood cells:** differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
- Clinical chemistry:
  - **Electrolytes**: sodium, potassium, calcium, chloride,
  - **Renal function**: creatinine, eGFR (Schwartz formula),
  - **Liver function**: total bilirubin, AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), ALP (Alkaline phosphatase).
- C-peptide (Visit 3, Day 1);

Technical formulas are described in Section 2.5.1.

2.1.4.6 Vital signs variables

Vital signs include: BMI percentile, systolic and diastolic blood pressure (mmHg) and heart rate (beats per minute).

2.1.4.7 Tanner puberty stage variables

Tanner puberty stage (pre-pubertal, adolescent, adult) will be analyzed.

2.1.4.8 Immunogenicity variables

The evaluation of anti-insulin antibodies (AIA), corresponding more specifically to anti-insulin glargine antibodies, will consist of:

- AIA status: positive/negative/ inconclusive.
- AIA titer.
- Cross-reactivity to Human insulin: positive/negative/not evaluable.
- Pre-existing, treatment-induced, treatment-boosted.
- Relationship (yes or likely, no or unlikely) provided by the committee of experts, establishing the relationship of AIA to potential indicators of insulin resistance or to hypersensitivity events in patients with treatment-induced or treatment-boosted AIA. Definitions of potential indicators of insulin resistance, hypersensitivity events are provided in the Operation Manual for Blinded External Endpoint Assessment Committee of the study.

The following definitions will be used to identify patients with a change in AIA response during the on-treatment period (7):

- Patients with treatment-induced AIAs are defined as patients with AIAs that are developed de novo (seroconversion) following the IMP administration (ie, patients with at least one positive AIA sample at any time during the on-treatment period, in those patients without pre-existing AIA or with missing baseline sample).
- Patients with treatment-boosted AIAs are defined as patients with pre-existing AIAs that are boosted to a significant higher titer following the IMP administration (ie, patients with at least one AIA sample with at least a 4-fold increase in titers compared to baseline value at any time during the on-treatment period, in those patients with pre-existing AIA).

Patients with treatment-emergent AIA (Yes, No) will be derived as follows:

- Patients with treatment-emergent AIAs (AIA incidence) are defined as patients with treatment-induced or treatment-boosted AIAs.
- Patients without treatment-emergent AIAs are defined as patients without treatment-induced or treatment-boosted AIAs.
- Inconclusive patients (patients who could not irrefutably be classified as patients without treatment-emergent AIAs are not included in the above categories and are listed separately.

Treatment-emergent AIAs at last on-treatment value (Yes, No) is also derived, using the same definitions based on results obtained at the last on-treatment visit (ie, taking into account the closest value prior to the last dose of IMP).

For patients with treatment-induced and treatment-boosted AIAs, the peak titer is defined as the maximal titer observed during the on-treatment period and the kinetics of AIA response is further classified as follows:

- Transient AIA response, defined as a response detected only at one sampling time point during the on-treatment period (excluding the last sampling time point); or response detected at two or more sampling time points during the on-treatment period, where the first and last AIA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the patient's last sampling time point is AIA-negative.
- Persistent AIA response, defined as a response detected at two or more sampling time points during the on-treatment period, where the first and last AIA-positive on-treatment sample (irrespective of any negative samples in between) are separated by at least 16 weeks; or response detected in the last two sampling time points, irrespective of the time period in between.
- Indeterminate AIA response, defined as a response where only the last sampling time point is positive and all previous samples are negative.

2.1.5 Pharmacokinetic variables

The plasma concentration of insulin glargine will be analyzed by the six time points based on relative time from PK date/time to last IMP injection date/time. The analyses windows considered for the analyses are provided in Section 2.5.4.

Basal insulin dosing regimen	Time point
Morning	Pre-dose
	4h post-dose
	8h post-dose
Evening	12h post-dose
	16h post-dose
	20h post-dose

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.

Randomized patients consist of all screened patients with a randomized treatment allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not.

The total number of patients for each of the following categories will be presented in the CSR of the main 6-month period and in the CSR of the 12-month study period separately, using a flow-chart diagram or summary tables:

- Screened patients: all patients who have originally met inclusion criteria and have signed the informed consent.
- Screen failure patients and reason for screen failure.
- Randomized patients: all screened patients with a treatment arm allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment was used or not.
- Treated but not randomized patients.
- Randomized but not treated patients.
- Randomized and treated patients.
- The intent-to-treat (ITT) population (as defined in Section 2.3.1.1, analyzed as randomized):
  - The randomization strata (screening HbA1c categories [<8.5%, ≥8.5%] and age group at screening visit [<12 years and ≥12 years] assigned by IVRS/IWRS will be summarized. The discrepancy between the strata assigned by IVRS/IWRS and the information reported on e-CRF will be listed for all randomized patients.
- Disposition for the main 6-month period:
  - Patients who completed the main 6-month treatment period (patients who have performed Visit 14 [Week 26] and who did not permanently discontinue treatment),
  - Patients who completed the main 6-month study period (patients who have performed Visit 14 [Week 26]),
  - Patients who permanently discontinued the IMP during the main 6-month treatment period, and the reasons for permanent treatment discontinuation,

  - Patients who permanently discontinued the study during the main 6-month period, and the reasons for permanent study discontinuation,
  - Patient's decision for treatment discontinuation decision for treatment discontinuation during the main 6-month period,
  - Status at last study contact of patients who permanently discontinued the treatment during the main 6-month period.
- Disposition for the main 12-month period:
  - Patients who completed the 12-month treatment period (patients who have performed Visit 18 [Week 52] and who did not permanently discontinue treatment),
  - Patients who completed the main 12-month study period (patients who have performed Visit 18 [Week 52]),
  - Patients who permanently discontinued the IMP during the 12-month treatment period, and the reasons for permanent treatment discontinuation,
  - Patients who permanently discontinued the study during the 12-month period, and the reasons for permanent study discontinuation,
  - Patient's decision for treatment discontinuation decision for treatment discontinuation during the main 12-month period,
  - Status at last study contact of patients who permanently discontinued the treatment during the main 12-month period.

For all categories of patients except the screened, screened failure and treated not randomized patients, percentages will be calculated using the number of randomized patients as denominator for different treatment groups.

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

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

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

Kaplan-Meier (KM) plots/estimates of the cumulative incidence of IMP discontinuation due to any reason, or due to AE, will be provided for the main 6-month and for the 12-month on-treatment period separately. Time to treatment discontinuation will be defined as the number of days from the first dose of IMP until the day of treatment discontinuation. All completers will be considered as censored observations. The censoring time will be the number of days from the first dose of IMP until the last dosing date.

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

- Efficacy population: intent-to-treat (ITT) population.
- Safety population.
- PK 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 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 who are dispensed study drug without calling the IVRS or before calling the IVRS are considered nonrandomized 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.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the intent-to-treat (ITT) population, as defined in the protocol.

2.3.1.1 Intent–to-treat population

The ITT population includes all randomized patients regardless of whether a treatment kit was used, and analyzed according to the treatment group allocated by randomization.

2.3.2 Safety population

The safety population is defined as the randomized population who actually received at least 1 dose or part of a dose of the 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.

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 and analyzed according to the randomized treatment.
- Patients receiving more than 1 IMP during the trial will be analyzed in the treatment group in which he/she was treated longer.

2.3.3 PK population

All patients randomized and treated patients who provided at least one PK measurement will be included in the PK population.

2.4 STATISTICAL METHODS

Continuous data will be summarized by treatment group using the number of available observations (N), mean, standard deviation (SD), minimum, median and maximum.

Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from baseline) by scheduled post-baseline visits will be provided on observed cases, ie, the inclusion of only patients having non-missing assessments at a specific visit. All statistical analyses (descriptive statistics, plots, and statistical models) will be performed on visits defined using the time windows provided in Section 2.5.4.

2.4.1 Demographics and baseline characteristics

Parameters will be summarized on the randomized population and analyzed in the treatment group to which patients were randomized.

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

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.

2.4.2 Prior or concomitant medications

The prior, concomitant and post-treatment medications will be presented for the randomized population separately for anti-diabetic medications and other (i.e non-anti-diabetic) medications.

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 times for the same medication.

The tables for prior other medications will be sorted by decreasing frequency of anatomic class followed by therapeutic class (ATC2) based on the overall incidence across treatment groups. In case of equal frequency, alphabetical order will be used.

The table for prior anti-diabetic medications will be sorted by decreasing frequency of pharmacological class (ATC3) followed by chemical class (ATC4) and standardized medication name based on the overall incidence across treatment groups. In case of equal frequency, alphabetical order will be used.

The tables for concomitant and post-treatment other medications will be sorted by decreasing frequency of anatomic class followed by therapeutic class (ATC2) based on the incidence in the HOE901-U300 group. In case of equal frequency, alphabetical order will be used.

The tables for concomitant and post-treatment anti-diabetic medications will be sorted by decreasing frequency of pharmacological class (ATC3) followed by chemical class (ATC4) and standardized medication name based on the incidence in the HOE901-U300 group. In case of equal frequency, alphabetical order will be used.

Frequency statistics including number of patients and percentage will be provided. No statistical test for the between-group difference will be performed.

The prohibited medications will be presented by prohibited medication category as defined in deviation and by standardized medication name.

Medications will be presented for the main 6-month and for the 12-month study period separately.

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 in the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

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

The duration of exposure to the IMP during the study will be the total number of days of administration of IMP, ignoring temporary drug discontinuation (see Section 2.5.1 for calculation in case of missing or incomplete data), and is defined as:

(Date of the last IMP administration – date of the first IMP administration) + 1

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- Up to 2 weeks.

- >2 to 4 weeks.
- >4 to 8 weeks.
- >8 to 12 weeks.
- >12 to 16 weeks.
- >16 to 20 weeks.
- >20 to 25 weeks.
- >25 to 26 weeks.
- >26 to 38 weeks.
- >38 to 51 weeks.
- >51 to 52 weeks.
- >52 weeks.

The exposure parameters will be provided for the main 6-month on-treatment period and for the 12-month on-treatment period, respectively.

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.

2.4.3.2 Daily insulin doses

Daily insulin doses for the main 6-month period and 12-month period

The process described in Section 2.5.4 will be applied to assign visits to the insulin doses transferred from the e-diary into the clinical database, and to retrieve doses in case of premature treatment discontinuation.

At each visit, the average daily basal, mealtime, and total (basal plus mealtime) insulin doses (U and U/kg body weight) will be calculated as the mean of daily insulin doses collected in the week before the visit. Technical details related to the computation and handling of missing data are described in Section 2.5.3.

The daily insulin doses (basal, mealtime, total) will be described at each visit, as well as the changes from baseline, relative change from baseline and change from previous visit.

The calculation of daily insulin doses at baseline is defined in Section 2.1.1.

Daily insulin doses for the post-treatment period (4-week follow-up)

Insulin dose after switch-back to a non-study therapy during the initial four weeks after change over from the study treatment will be evaluated.

A summary table will be provided for anti-diabetic therapies taken during the follow-up period based on WHO-DD coding.

Observed value and change in daily basal insulin dose (U and U/kg body weight) from the 4-week follow-up baseline (end of treatment: Month 12) to visit 20 will be calculated.

During the post-treatment period (4-week follow-up) the change in daily basal/mealtime/total insulin, evaluated between the day following last IMP intake and visit 20, will be the average daily insulin doses computed on a weekly basis. In case of any missed doses, corresponding days are not to be taken into account in the determination of the average daily insulin doses.

Descriptive statistics will be provided for the above variables based on safety population.

2.4.3.3 Compliance

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

Percentage of compliance for a patient will be defined as the exposure duration of study minus number of days with a dose equal to 0 divided by the duration of the IMP exposure.

Treatment compliance will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized.

Cases of symptomatic overdose with IMP/NIMP will be listed as such in Section 2.4.5.3. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

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

Analyses windows considered for the analysis of HbA1c and FPG endpoints are defined in Section 2.5.4.

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 26 in % as defined in Section 2.1.3.1) will be analyzed for non-inferiority assessment, in the ITT population using post-baseline HbA1c data available on the main 6-month randomized period (defined in Section 2.1.3, ITT estimand).

A multiple imputation approach will be used where missing data from patients who do not adhere to IMP will be represented by the data from those patients in the same treatment group who also do not adhere to IMP but have the measurement for the primary endpoint. Details of the proposed multiple imputation analysis in two parallel parts (according the status of the patients), are provided below:

Part1: Imputation for missing data in patients who prematurely discontinued IMP during the main 6-month treatment period

Missing data in patients who prematurely discontinued IMP during the main 6-month treatment period will be imputed using a model estimated solely from data observed in other patients who prematurely discontinue IMP during the main 6-month treatment period and have change in HbA1c available at Week 26. Due to the anticipated small number of these latter patients, a basic imputation model will be built, including only the treatment group as predictor. Missing data will be imputed using the regression method.

Part2: Imputation for missing data in patients who complete the main 6-month treatment period

Missing data in patients who complete the main 6-month treatment period will be imputed separately, using a model estimated from data observed in other patients who complete the main 6-month treatment period and have change in HbA1c available at Week 26. 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. The imputation model will include the continuous fixed covariates of the baseline HbA1c value as well as the changes from baseline in HbA1c at Week 12 and Week 26.

- Step 2: using the monotone data set from step 1, missing data will be imputed using the regression method. The imputation model will include the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years) as well as the continuous fixed covariates of the baseline HbA1c value and the changes from baseline in HbA1c at Week 12 and Week 26.

Missing values will be imputed 1,000 times. Completed datasets from the two parts detailed above will be combined into a single dataset. Each completed dataset will be analyzed using an analysis of covariance (ANCOVA) of change from baseline to Week 26 in HbA1c, including the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), as well as the continuous fixed covariates of the baseline HbA1c value. The final results will be obtained by combining the least squares means and least squares mean differences from these 1,000 analyses, using Rubin's formula.

This model will provide baseline adjusted least squares (LS) means estimates at Week 26 for both treatment groups, as well as, the differences of these estimates, with their corresponding SEs and 95% CIs. These values will be calculated using adequate contrasts at Week 26, based on the

observed proportions of patients in the randomization stratum and the observed baseline mean HbA1c in the ITT population.

Programming procedure is detailed in Appendix A.

The primary efficacy variable will be assessed for non-inferiority for the primary efficacy analysis. To assess non-inferiority of HOE901-U300 versus Lantus, the upper bound of the two-sided 95% CI (Confidence Interval) for the difference in the mean change in HbA1c from baseline to endpoint (Month 6) between HOE901-U300 and Lantus on ITT population will be compared with the predefined non-inferiority margin of 0.3%. Non-inferiority will be demonstrated if this upper bound is <0.3%.

Only if non-inferiority of HOE901-U300 versus Lantus is demonstrated, superiority of HOE901-U300 over Lantus in HbA1c change from baseline to Week 26 will be assessed. Superiority of HOE901-U300 over Lantus 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 26 between HOE901-U300 and Lantus is < 0. The superiority comparison is considered as a secondary analysis of the primary efficacy variable.

The tests for the primary endpoint (Week 26) will be performed one-sided at level $\alpha = 0.025$.

2.4.4.1.2 Description of missing data

Missing data in the primary efficacy analysis:

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

- As described in Section 2.2, Kaplan-Meier plots/estimates of the cumulative incidence of IMP discontinuation will be provided by treatment group, with hazard ratio and 95% CI estimated using Cox regression model.
- 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 main 6-month randomized period,
  - Pattern 3: patients with baseline and at least one post-baseline value during the main 6-month randomized period but not at Week 26,
  - Pattern 4: patients with baseline and Week 26 value during the main 6-month randomized period.
- Baseline characteristics and HbA1c values by visit will be presented by missing data pattern for each treatment group, using descriptive statistics and/or graphs.

Further exploratory analyses will be performed to evaluate factors influencing missing data: for each baseline characteristic, a logistic regression will be performed to model the missingness (Yes, No) at Week 26 (Visit 14). The model will include the treatment group, and the categorical or continuous covariate of the studied baseline characteristic. Estimates and p-value will be provided for descriptive purpose. A separate model will be run for each baseline characteristic; additional multivariate analyses may be performed if needed.

2.4.4.1.3 Supportive analysis

A supportive analysis of the primary efficacy analysis will be performed on the change in HbA1c from baseline to Month 6 in the ITT population, during the main 6-month on-treatment period (on-treatment estimand), as defined in Section 2.1.3. A multiple imputation approach will be used as described below.

Missing data, (ie, all patients without change from baseline HbA1c at Week 26 during the main 6-month on-treatment period) will be imputed using a model estimated from data observed in other patients who have change in HbA1c at Week 26. 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. The imputation model will include the continuous fixed covariates of the baseline HbA1c value as well as the changes from baseline in HbA1c at Week 12 and Week 26.
- Step 2: using the monotone data set from step 1, missing data will be imputed using the regression method. The imputation model will include the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years) as well as the continuous fixed covariates of the baseline HbA1c value and the changes from baseline in HbA1c at Week 12 and Week 26.

Missing values will be imputed 1,000 times. Each completed dataset will be analyzed using an analysis of covariance (ANCOVA) of change from baseline to Week 26 in HbA1c, including the fixed categorical effects of treatment group, randomization stratum of age group at screening visit (<12 years and ≥12 years), as well as, the continuous fixed covariate of the baseline HbA1c value. The final results will be obtained by combining the least squares means and least squares mean differences from these 1,000 analyses, using Rubin's formula.

This model will provide baseline adjusted least squares (LS) means estimates at Week 26 for both treatment groups, as well as, the differences of these estimates, with their corresponding SEs and 95% CIs. These values will be calculated using adequate contrasts at Week 26, based on the observed proportions of patients in the randomization stratum and the observed baseline mean HbA1c in the ITT population.

2.4.4.1.4 Sensitivity analysis to handle missing data

Sensitivity analysis will be conducted to assess the robustness of primary efficacy analysis with regard to missing data (8).

Tipping point analysis

In order to assess the impact of missing data, a tipping-point analysis based on the pattern mixture model approach will be performed as below.

The considered pattern mixture model will introduce a sensitivity parameter, δ, corresponding to the difference in mean change from baseline in HbA1c between patients with missing data and patients with observed data.

The change in HbA1c from baseline to Month 6 in % using HbA1c values during the main 6-month randomized period (all post baseline available data), will be analyzed in the ITT population using a multiple imputation approach. Missing data (ie, all patients without change from baseline HbA1c at Week 26 during the main 6-month randomized period) will be imputed using a model estimated from data observed in other patients who have change in HbA1c at Week 26.

Missing data will be imputed 1,000 times to generate 1,000 complete data sets with the 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. The imputation model will include the continuous fixed covariates of the baseline HbA1c value as well as the changes from baseline in HbA1c at Week 12 and Week 26.
- Step 2: using the monotone data set from step 1, missing data will be imputed using the regression method. The imputation model will include the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years) as well as the continuous fixed covariates of the baseline HbA1c value and the changes from baseline in HbA1c at Week 12 and Week 26.

The imputed change HbA1c at Week 26 in the HOE901-U300 group will then be penalized by adding δ to the change whereas the imputed change HbA1c in the Lantus group will not be penalized (δ = 0 corresponds to the MAR assumption).

The 1,000 complete data sets will then be analyzed using an analysis of covariance (ANCOVA) model including the fixed categorical effects of the randomization stratum of age group at screening visit (<12 years and ≥12 years), the treatment group, as well as, the continuous fixed covariate of the baseline HbA1c value. The MIANALYZE procedure will then be used to generate valid statistical inferences by combining results from the 1,000 analyses using Rubin's formulae.

This procedure will provide baseline adjusted least-squares means estimates at Week 26 for both treatment groups, as well as, the differences of these estimates, with their corresponding SEs and 95% CIs.

To investigate how the conclusions depend on the adopted values of δ, the testing will be repeated over a range of plausible values for δ, the treatment effect being penalized by a positive value and favored by a negative value.

A specific illustration on the value of the minimum penality leading to a non-rejection of the null hypothesis (confidence interval upper limit greater than 0.3%) will be provided (9).

2.4.4.1.5 Subgroup analyses

The primary efficacy endpoint will be further analyzed to examine whether the treatment effect varies in subgroups defined by the following baseline covariates, list not exhaustive:

- Randomization strata of age group (<12, ≥ 12 years of age).
- Randomization strata of screening HbA1c categories (<8.5; ≥8.5%).
- Gender (Male, Female).
- Race (Caucasian/White, Black, Asian/Oriental, Other).
- Ethnicity (Hispanic, not Hispanic).
- Regions (North America, South/Latin America, Western Europe, Eastern Europe, Rest of the World [ROW]).
- Baseline BMI percentile: <5th percentile; 5th-<85th percentile; 85th-<95th percentile; ≥95th percentile.
- Baseline Tanner puberty stage evaluation (pre-pubertal, adolescent, adult).
- Baseline Estimated GFR categories (mL/min/1.73m²): (<30; [30-60[; ≥60).
- Duration of diabetes (<2; [2 - 5[; ≥5 years).

For each subgroup, the primary efficacy variable will be analyzed in the ITT population. The same multiple imputation approach as described for primary analysis will be applied, using 1,000 completed datasets generated for the primary analysis. Each completed dataset will be analyzed using an ANCOVA of change from baseline to Week 26 in HbA1c, including the fixed categorical effects of the treatment group, randomization stratum of age group at screening visit (<12 years and ≥12 years), the continuous fixed covariate of the baseline HbA1c value, and adding the corresponding subgroup factor and subgroup factor-by-treatment interaction. The final results will be obtained by combining the LS means and LS mean differences within each subgroup from these 1,000 analyses, using Rubin's formula.

When the subgroup considered is equal to the randomization strata of age group (<12; ≥12), the categorical stratum of age group will be removed from the model.

When the subgroup considered is equal to the randomization strata of screening HbA1c (<8.5, ≥8.5%), the baseline HbA1c value will be removed from the model.

Least Square Means Difference versus Lantus at Week 26 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 26 will also be provided for each factor for purpose flagging the subgroups where the treatment difference does not seem to be homogeneous. Forest plots will be provided for a better visual evaluation.

HbA1c by randomization stratum of age at screening (<12 years and ≥12years)

In each, subgroup defined by randomization stratum of age at screening (<12 years and ≥12years), summary statistics (including number, mean, median, standard deviation, minimum and maximum) of primary efficacy endpoint (estimated values and changes from baseline following multiple imputation approach for each visit) and adjusted least-squares means estimates will be presented at each visit by treatment group using tables and graphs. The differences of these estimates versus Lantus, with their corresponding associated standard errors and 95% confidence intervals will also be calculated.

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

2.4.4.1.6 Assessment of treatment effect at 12 months

The change in HbA1c from baseline to Week 52 will be described in the ITT population, using all post-baseline HbA1c data available during the 12-month randomized period.

For descriptive purpose, the treatment effect at Week 52 will be evaluated using the same multiple imputation approach as for primary analysis (Section 2.4.4.1.1) and as described below for the two parallel parts.

Missing data in patients who prematurely discontinued IMP during the main 12-month treatment period will be imputed using a model including only the treatment group as predictor (Part 1).

Missing data in patients who complete the 12-month treatment period will be imputed in step 1 using a model including the continuous fixed covariates of the baseline HbA1c value as well as the changes from baseline in HbA1c at Week 12, Week 26, Week 38 and Week 52, and in step 2 using a model including the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years) as well as the continuous fixed covariates of the baseline HbA1c value and the changes from baseline in HbA1c at Week 12, Week 26, Week 38 and Week 52 (Part 2).

2.4.4.2 Analyses of secondary efficacy endpoints

Secondary efficacy endpoints defined in Section 2.1.3.2 will be analyzed in the ITT population, using all post-baseline data available during the main 6-month randomized period.

All secondary endpoints will be also described at end of the 12-month randomized period (Week 52).

2.4.4.2.1 Continuous endpoints

Change from baseline in FPG at Week 26 and at Week 52 will be analyzed using a similar multiple imputation in two parallel parts, as described before for the primary efficacy endpoint, adding screening HbA1c (<8.5%; ≥8.5%) in Part 2, step 2 imputation model (ie, for missing data in patients who complete the main 6-month treatment period).

- At week 26,
  - Missing data in patients who prematurely discontinued IMP during the main 6-month treatment period will be imputed using a model including only the treatment group as predictor (Part 1),
  - Missing data in patients who complete the main 6-month treatment period will be imputed in step 1 using a model including the continuous fixed covariates of the baseline FPG value and the change from baseline in FPG at Week 12 and Week 26, in step 2 using a model including the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), randomization strata of screening HbA1c (<8.5, ≥8.5%) as well as the continuous fixed covariates of the baseline FPG value and the changes from baseline in FPG at Week 12 and Week 26 (Part 2).
- At week 52,
  - Missing data in patients who prematurely discontinued IMP during the 12-month treatment period will be imputed using a model including only the treatment group as predictor (Part 1),
  - Missing data in patients who complete the 12-month treatment period will be imputed in step 1 using a model including the continuous fixed covariates of the baseline FPG value as well as the changes from baseline in FPG at Week 12, Week 26, Week 38 and Week 52, in step 2 using a model including the fixed categorical effects of the treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), the randomization strata of screening HbA1c (<8.5, ≥8.5%) as well as the continuous fixed covariates of the baseline FPG value and the changes from baseline in FPG at Week 12, Week 26, Week 38 and Week 52 (Part 2).

The other continuous endpoints listed below will be analyzed with an ANCOVA model and descriptively with mean, median, SD, minimum and maximum for values and for changes from baseline and will be presented by treatment group for each visit.

- Change from baseline in 24-hour mean plasma glucose based on 8-point SMPG profiles at Week 26 and Week 52.
- Change from baseline in variability of 24-hour mean plasma glucose based on 8-point SMPG profiles at Week 26 and Week 52.
- Change from baseline in 8-point self-monitored plasma glucose (SMPG) profiles per time-point (pre-prandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, bedtime plasma glucose, nocturnal plasma glucose) at Week 26 and Week 52. The analysis will be performed taking into account the time-points corrected by the investigator in the e-CRF.
- Change from baseline in average pre-breakfast SMPG at Week 26 and at Week 52.

The ANCOVA model will include treatment, randomization stratum of screening HbA1c (<8.5 and ≥8.5%), and randomization stratum of age group at screening visit (<12 years and ≥12 years), and the baseline value as a covariate. For change in variability of the 24-hour mean plasma glucose, an ANOVA model with treatment, randomization stratum of screening HbA1c (<8.5 and ≥8.5%), and randomization stratum of age group at screening visit (<12 years and ≥12 years) will be used. The adjusted treatment mean estimates with standard errors, the adjusted estimate of treatment mean difference (between HOE901-U300 and Lantus) with standard error, and associated 95% confidence interval will be provided.

Observed values and change from baseline in average pre-breakfast SMPG will be also described for all visits (on-site and phone visits) with mean, median, SD, minimum and maximum. A figure representing the mean (+/- SE) change from baseline at each visit will be produced by treatment group.

2.4.4.2.2 Categorical endpoints

The categorical efficacy parameters (percentage of patients with HbA1c <7.5% and percentage of patients with FPG ≤130 mg/dL (7.2 mmol/L)) will be analyzed by using Cochran-Mantel-Haenszel (CMH) method with treatment as factors, stratified by randomization stratum of HbA1c (<8.5%, ≥8.5%) and by randomization stratum of age group (<12 years and ≥12 years) at screening.

The analyses will be performed:

- At Week 26.
- At Week 26 and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) hypoglycemia during the last 3 months of the main 6-month randomized period.

95 % confidence interval for the treatment difference or ratios will be provided.

If any table cell frequency in a stratum is zero, continuity correction (10) will be applied.

Patients, who have prematurely discontinued the study and without any available hypoglycemia event during the study period, will be considered as a failure, ie, having a hypoglycemia event.

2.4.4.3 Multiplicity issues

In order to handle the multiple comparisons of the non-inferiority and then the superiority of HOE901-U300 over Lantus, corresponding respectively to the primary efficacy analysis and a secondary analysis of the primary efficacy variable, the type-I error will be controlled by the use of the sequential inferential approach. Only if non-inferiority is demonstrated, superiority of HOE901-U300 over Lantus of the mean change from baseline to Month 6/ Week 26 in HbA1c will be assessed. The tests for the primary endpoint (Week 26) will be performed one-sided at level $\alpha = 0.025$.

The other secondary efficacy variables will be analyzed for exploratory purpose only.

2.4.4.4 Additional efficacy analyses

No additional efficacy analyses are planned.

2.4.5 Analyses of safety data

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

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. When the time of assessment is not available, the value is considered as baseline if assessment date is the date of 1st IMP intake.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs (PCSA criteria will be provided in the ADaM metadata).
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE 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 central laboratory/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 defined 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 one prior to the last dose intake.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. Relative risks versus Lantus and their 95% confidence intervals may be provided, if relevant.

2.4.5.1 Analyses of Hypoglycemia events

All analyses of hypoglycemia events will be performed on the safety population, separately on events occurring during the main 6-month TEAE period (for the main 6-month CSR) and during the 12-month TEAE period (for the 12-month CSR) (as defined in Section 2.1.4). The analyses planned to be done by treatment period will include also the analyses performed by the following periods: from first injection of IMP to end of Week 8, from start of Week 9 to Month 6, post-treatment period (depending on the CSR, at 6 month or 12 month) (as defined in Section 2.1.4.1).

Incidence of patients with at least one hypoglycemia event

- Incidence of patients with at least one hypoglycemia event and 95% CI estimated by Clopper-Pearson exact method, will be presented for any hypoglycemia and for each hypoglycemia category, overall and by time of the day (as described in Section 2.1.4.1).
- Incidence of patients with at least one hypoglycemia event and 95% CI estimated by Clopper-Pearson exact method, will be presented by treatment period (as described in Section 2.1.4.1) for any hypoglycemia and for each hypoglycemia category (except probable, pseudo), overall and by time of the day.
- For any hypoglycemia and for each hypoglycemia category (except probable, pseudo), incidence of patients with at least one hypoglycemia will be compared, overall and by treatment period (except post-treatment period), for HOE901-U300 versus Lantus using a CMH method with treatment group as a factor and stratified on randomization strata (screening HbA1c (<8.5%, ≥8.5%); age group (<12, ≥ 12 years of age)). If any table cell frequency in a stratum is zero, continuity correction (10) will be applied. Relative risk and 95% CI will be displayed using forest plots. This analysis will be done also for nocturnal (00:00 to 05:59 a.m. hours) hypoglycemia.
- Incidence of patients with at least one severe and/or documented (≤70 mg/dL and <54 mg/dL) hypoglycemia event will be summarized by hour of the day. Histograms will be provided.
- Incidence of patients with at least one severe and/or documented (≤70 mg/dL and <54 mg/dL) hypoglycemia event will be presented over time. Percentages will be calculated using the number of patients at risk at the beginning of each month. Histograms will be provided. This analysis will be done for any time of the day and for the nocturnal (00:00 to 05:59) period.
- Incidence of patients with at least one severe hypoglycemia event will be summarized by hour of the day. Histograms will be provided.
- Incidence of patients with at least one severe hypoglycemia event will be presented over time. Percentages will be calculated using the number of patients at risk at the beginning of each month. Histograms will be provided. This analysis will be done for any time of the day and for the nocturnal (00:00 to 05:59) period.
- Incidence of patients with at least one severe hypoglycemia event will be summarized by symptom, overall and by time of the day.

- Incidence of patients with at least one severe and/or documented (≤70 mg/dL and <54 mg/dL) hypoglycemia will be presented by subgroup and will be compared by subgroup for HOE901-U300 versus Lantus using a CMH method with treatment group as a factor and stratified on randomization strata (screening HbA1c (<8.5%, ≥8.5%); age group (<12, ≥ 12 years of age) if it is not a subgroup factor. If any table cell frequency in a stratum is zero, continuity correction (10) will be applied. The treatment-by-subgroup factor interaction will be tested for descriptive purpose using a logistic regression model with the corresponding subgroup, treatment, randomization strata and the interaction treatment-by-subgroup factor. Forest plots will be provided. The following subgroups will be displayed:
  - Randomization stratum of screening HbA1c (<8.5%, ≥8.5%),
  - Randomization stratum of screening of age group (<12, ≥ 12 years of age),
  - Gender (male, female),
  - Baseline tanner puberty stage evaluation (pre-pubertal, adolescent, adult),
  - Baseline BMI percentiles (<5th percentile; 5th-<85th percentile; 85th-<95th percentile; ≥95th percentile),
  - Baseline pre-breakfast SMPG,
  - These subgroup analyses will be done for any time of the day and for the nocturnal (00:00 to 05:59) period.
- Further subgroup analyses may be performed if deemed necessary for interpretation of results.

Number and rate of hypoglycemia event

- Number and rate of hypoglycemia event per patient-year will be summarized for any hypoglycemia and for each hypoglycemia category, overall and by time of day (as described in Section 2.1.4.1). Non classified hypoglycemia will be displayed.
- Number and rate of hypoglycemia event per patient-year will be presented by treatment period (as described in Section 2.1.4.1) for any hypoglycemia and for each hypoglycemia category (except probable, pseudo), overall and by time of the day.
- For any hypoglycemia and for each hypoglycemia category (except probable, pseudo), the number of hypoglycemia events per patient-year will be compared, overall and by treatment period (except post-treatment period), for HOE901-U300 versus Lantus using a negative binomial regression model with a log-link function, and the logarithm of the treatment-emergent analyzed period as offset. The model will include the treatment group and randomization strata (screening HbA1c (<8.5%, ≥8.5%); age group (<12, ≥ 12 years of age)). If the negative binomial model does not converge (e.g., due to sparse data), randomization strata may be removed from the model. Relative risk and 95%CI will be displayed using forest plots. This analysis will be done also for nocturnal (00:00 to 05:59 am hours) hypoglycemia.

- Cumulative number and rate of severe and/or documented (≤70 mg/dL and <54 mg/dL) hypoglycemia event per 100 patient-days will be summarized by hour of the day. Figures will be provided. Same analysis will be done for severe hypoglycemia.
- Cumulative mean number of severe and/or documented (≤70 mg/dL and <54 mg/dL) hypoglycemia will be summarized over time using Nelson-Aalen estimates. Figures will be provided. This analysis will be done also for nocturnal (00:00 to 05:59 am hours) severe and/or documented (≤70 mg/dL and <54 mg/dL) hypoglycemia. Same analyses will be done for severe hypoglycemia.

Hypoglycemia data from the external committee

Incidence of patients with at least one hypoglycemia event qualifying for review by the external committee will be summarized, and among these, proportion of patients with at least one hypoglycemia event classified as severe by the external committee will be presented overall, by treatment period (except the post-treatment period), over time (by month) and by time of the day (as described in Section 2.1.4.1). Number and rate of hypoglycemia events per patient-year qualifying for review by the external committee will be summarized overall, by treatment period (except post-treatment period) and by time of the day, and among these, the number and rate of hypoglycemia events classified as severe by the external committee per patient-year.

2.4.5.2 Analyses of Hyperglycemia with ketosis

All analyses of hyperglycemia with ketosis events will be performed on the safety population, separately on events occurring during the main 6-month and 12-month TEAE periods (as defined in Section 2.1.4). The analyses planned to be done by treatment period will include also the analysis performed for the post-treatment period for the 12-month CSR (as defined in Section 2.1.4.2).

All analyses of hyperglycemia with ketosis events will be done for categories of hyperglycemia with ketosis defined in Section 2.1.4.2.

Incidence of patients with at least one hyperglycemia with ketosis event

- Incidence of patients with at least one hyperglycemia with ketosis event and 95% CI estimated by Clopper-Pearson exact method, will be presented overall and by treatment period.
- Incidence of patients with at least one hyperglycemia with ketosis event and 95% CI estimated by Clopper-Pearson exact method, will be also presented by subgroup for HOE901-U300 versus Lantus. The following subgroups will be displayed:
  - Randomization stratum of screening HbA1c (<8.5%, ≥8.5%),
  - Randomization stratum of screening of age group (<12, ≥ 12 years of age),
  - Gender (male, female),
  - Baseline tanner puberty stage evaluation (pre-pubertal, adolescent, adult),

- Baseline BMI percentiles (<5th percentile; 5th-<85th percentile; 85th-<95th percentile; ≥95th percentile),
- Baseline pre-breakfast SMPG.

Number and rate of hyperglycemia with ketosis event

- Number and rate of hyperglycemia with ketosis events per patient-year will be summarized overall, by treatment period.
- Cumulative mean number of hyperglycemia with ketosis will be summarized over time using Nelson-Aalen estimates. Figures will be provided.

In case of too few patients with hyperglycemia with ketosis and/or events of hyperglycemia with ketosis, some of the analyses described above may not be done and may be replaced by listings.

Analyses of hyperglycemia with ketosis adverse events will be included in the analysis of the other TEAEs as described in the Section 2.4.5.3.

2.4.5.3 Analyses of adverse events

Generalities

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

All adverse events will be reported for the main 6-month TEAE period and for the 12-month TEAE period separately.

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 will be the safety population within each treatment group.

Sorting within tables should ensure the same presentation for the set of all AEs within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by internationally agreed order of SOC and decreasing frequency of PTs within SOC will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the HOE901-U300 treatment arm.

Analysis of all TEAE(s)

The following TEAE summaries will be generated for the safety population:

- Overview of TEAEs, summarizing number (%) of patients with any:
  - TEAE,
  - Serious TEAE,
  - TEAE leading to death,
  - TEAE leading to permanent treatment discontinuation,

- All TEAEs by primary SOC, showing number (%) of patients with at least one TEAE, sorted by internationally agreed order of primary SOC.
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one TEAE sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT.
- All TEAEs by primary SOC and PT, showing number (%) of patients with at least one TEAE, sorted by SOC internationally agreed order and decreasing incidence of PTs within SOC. This sorting order will be applied to all other tables, unless otherwise specified.
- Number (%) of patients experiencing common TEAE(s) (HLT incidence ≥2% in any treatment group) presented by primary SOC, HLT, and PT, sorted by SOC internationally agreed order. The other levels (HLT, PT) will be presented in an alphabetic order. Analysis performed overall and by subgroup of age, race, gender.
- All TEAEs regardless of relationship and related to IMP by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one TEAE, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.
- All TEAEs by maximal severity, presented by primary SOC and PT, showing number (%) of patients with at least one TEAE by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.
- Number (%) of patients experiencing TEAE(s) presented by Primary and Secondary SOC, HLGT, HLT, and PT, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.

Analysis of all treatment-emergent SAE(s)

- All treatment-emergent SAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one serious TEAE, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.
- All treatment-emergent SAEs regardless of relationship and related to IMP by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one treatment-emergent SAE, sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.

Analysis of all TEAE(s) leading to treatment discontinuation

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

Analysis of TEAE(s) related to injection site reactions, hypersensitivity reactions

- All TEAEs related to injection site reactions or hypersensitivity reactions by PT, showing number (%) of patients sorted by decreasing incidence of PT in the HOE901-U300 treatment arm.
- All TEAEs related to injection site reactions, hypersensitivity reactions, regardless of relationship and related to IMP, by PT, showing number (%) of patients sorted by decreasing incidence of PT in the HOE901-U300 treatment arm.

Analysis of adverse events of special interest

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

Analysis of pre-treatment and post-treatment adverse events

- A listing of all pre-treatment and post-treatment AEs will be provided.

2.4.5.4 Deaths

The following deaths summaries will be generated on the safety population, during the main 6-month on-treatment period and for the 12-month on-treatment period separately:

- Number (%) of patients who died by study period (on-study, on-treatment, post-study) and reasons for death.
- All TEAEs leading to death (death as an outcome on the adverse event e-CRF page as reported by the investigator), by primary SOC, HLGT, HLT, and PT, showing number (%) of patients sorted by SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in an alphabetic order.
- A listing of all deaths.

2.4.5.5 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, each post-baseline time-point, last on-treatment value during the main 6-month and 12-month on-treatment periods) by treatment group. This section will be organized by biological function as specified in Section 2.1.4.5.

The incidence of PCSAs at any time during the main 6-month on-treatment period and during the 12-month on-treatment period will be summarized by biological function and treatment group whatever the baseline level and according to the following baseline status categories:

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

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter.

A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with elevated in bilirubin ≥2 x ULN) will be provided with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters: conjugated bilirubin and prothrombin time/international normalized ratio, creatine phosphokinase, serum creatinine, complete blood count.

The incidence of liver-related adverse events will be summarized by treatment group. The selection of preferred terms will be based on the hepatic disorder SMQ.

2.4.5.6 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum, and maximum) of all vital signs variables (raw values and changes from baseline) described in Section 2.1.4.6 will be calculated for each visit or study assessment (baseline, each post-baseline time-point, last on-treatment during the main 6-month and 12-month on-treatment periods) by treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized during the main 6-month and the 12-month on-treatment period 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 incidence of PCSAs at any time during the TEAE period will be summarized by treatment group whatever the baseline level and according to baseline status.

The change in BMI percentile from baseline will be analyzed in the safety population using an ANCOVA model including the treatment group, randomization strata, as well as the baseline BMI percentile value.

2.4.5.7 Analyses of Tanner puberty stage measurement

Tanner puberty stage (pre-pubertal, adolescent, adult) will be described using count and percentage.

2.4.6 Analyses of anti-insulin antibody data

The analyses of AIA data will be performed based on the safety population, for the main 6-month on-treatment period and for the 12-month on-treatment period separately.

The number and percentage of patients with anti-insulin glargine antibody positive and antibody negative sample will be summarized by treatment group and visit. Results at the last on-treatment visit will be also provided.

On the group of patients with anti-insulin glargine antibody positive sample at a given visit, anti-insulin glargine antibody titers will be summarized (using descriptive statistics by number (N), median, Q1, Q3, variation coefficient, minimum, maximum, geometric mean, SD, and 95% CI), and the number and percentage of patients with cross-reactivity to human insulin will be provided.

The number and percentage of patients will be provided by treatment group for each of the following categories:

- Patients with treatment-induced AIAs.
- Patients with treatment-boosted AIAs.
- Patients with treatment-emergent AIA (AIA incidence).
- Patients without treatment-emergent AIA.
- Patients with pre-existing AIAs or treatment-induced AIAs or treatment-boosted (AIA prevalence).

For patients with treatment-induced and treatment-boosted AIAs, the kinetics of AIA response (transient, persistent, or indeterminate AIA response as defined in Section 2.1.4.8) will be further summarized using number and percentage of patients, and the peak titer will be described using median, Q1 and Q3.

Theses analyses will be performed for the overall safety population and by AIA subgroup (as defined above).

In order to assess the relationship between immunogenicity and efficacy assessments, the change in HbA1c from baseline will be summarized by treatment-emergent AIA (Yes, No) and treatment-emergent AIA at last on-treatment value (Yes, No).

The following safety data will be also summarized descriptively by treatment-emergent AIA (Yes, No) and AIA incidence at last on-treatment value (Yes, No):

- Hypoglycemia (any, severe, documented symptomatic, and severe and/or documented, at any time and nocturnal).

- Common TEAEs (ie, with HLT ≥2%) and SAEs.
- Injection site and hypersensitivity reactions.

For hypoglycemia, the proportion of patients with at least one event in each category listed above will be compared between treatment groups using a logistic regression model. Odds-ratios and 95% CIs will be provided.

Plots of the rate per year of event in each category of hypoglycemia listed above will be provided.

Insulin doses will be also described by treatment-emergent AIA (Yes, No) and treatment-emergent AIA at last on-treatment value (Yes, No).

Box plot of the maximal AIA titer during the main 6-month on-treatment period and during the 12-month on-treatment period will be provided by treatment group and according to the treatment-emergent AIA status. Baseline characteristics, insulin doses, HbA1c, hypoglycemia data and hypersensitivity reactions as well as injection site reactions will be listed for patients with treatment-emergent AIA and maximal titer above or equal to the upper whiskers in the boxplot, defined as 1.5 times the interquartile range.

Analyses of data from the external committee:

Hypersensitivity events and potential indicators of insulin resistance in patients with treatment-induced or treatment-boosted AIA status and assessed by the Committee as mediated or likely mediated by AIA will be analyzed as below:

- Percentage of patients with treatment-induced or treatment boosted AIA and hypersensitivity TEAE, overall and by AIA-mediated assessment (yes/no).
- Percentage of patients with treatment-induced or treatment boosted AIA and potential indicators of insulin resistance, overall and by AIA-mediated assessment (yes/no).

2.4.7 Analyses of pharmacokinetic and pharmacodynamic variables

Plasma concentrations of insulin glargine will be summarized on the PK population, by time point and by treatment group using descriptive statistics by N, mean, SD, geometric mean, coefficient of variation, SEM, median, minimum, and maximum. Only samples within the analyses windows defined in the Section 2.5.4 will be included in the calculations. Individual data might be listed as deemed necessary.

These tables will be performed overall and by AIA status (positive/negative) of patients at Week 26. In case of no AIA value available at week 26, the patient will be excluded from this PK analysis by AIA status.

Plots for concentration time profiles will be provided as follows:

- Plots of mean (+/-SD) by treatment group: mean (+/-SD) calculated in the above summary table and including samples within the analyses windows defined in the Section 2.5.4

- Spaghetti plots with all individual data by treatment group, including all samples regardless of analyses windows.

Population PK modeling will be performed by the Pharmacokinetics, Dynamics and Metabolism (PKDM) group at Sanofi, which is not in the scope of this SAP and would be reported separately.

2.4.8 Analyses of quality of life/health economics variables

Not applicable.

2.5 DATA HANDLING CONVENTIONS

This section describes general rules for data handling conventions, especially for patients with missing data.

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.

First IMP

The first IMP is identified by the start date reported for the IMP exposure in the e-CRF.

Demographic formulas

Body Mass Index (kg/m²)= (Weight in kg) / (Height in meters)²

Body Mass Index percentile will be derived according the WHO Child Growth Standards (1). Details will be provided in the ADaM metadata.

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 basal insulin treatment (years) = (Date of informed consent – date of first dose of previous basal insulin+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 onset calculation.

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

HbA1c transformation

To transform HbA1c in % to mmol/mol, the following formula (11) is used:

IFCC = (10.93*NGSP) - 23.50

NGSP (National Glycohemoglobin Standardization Program network) corresponds to Hba1c (%) band IFCC (International Federation of Clinical Chemistry network) to HbA1c (mmol/mol)

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 hyperglycemia with ketosis event per patient-year

Computed as [sum of number of episodes of hyperglycemia 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.

Estimated Glomerular Filtration Rate (eGFR) derived using Schwartz formula

Estimated Glomerular Filtration Rate (eGFR) by Schwartz = 0.413 x (Height/Enzymatic Serum Creatinine)

Where:

eGFR is reported as ml/min/SSA (#)

Height is reported in cm (#.#)

Enzymatic Serum Creatinine is reported in mg/dL

= Numerical value entered with number of significant digits

For purposes of reporting in our system 1.73m^2 has been given the unit of SSA, which is short for Standard Surface Area.

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

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.

Derived variables are considered missing if the original variables required to calculate them are missing. For example, if either a baseline assessment or an endpoint assessment is missing for a particular patient, then the change from baseline at endpoint is missing. Depending upon the assessment, analyses may not include all patients in the analysis population, because certain patients in the intended population may have missing data.

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 e-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 e-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

No imputation of adverse event/hypoglycemia dates/times will be performed.

By default all adverse events/hypoglycemia are emergent except if additional information allows to classify otherwise.

Handling of adverse events/hypoglycemia, laboratory data, vital signs 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/hypoglycemia that occurred on or after the day of randomization should be considered as treatment-emergent adverse events/hypoglycemia. The exposure duration should be kept as missing.

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; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

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

Handling of missing data in the calculation of HbA1c responders, FPG responders

For HbA1c responders (defined by HbA1c<7.5% overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) hypoglycemia during the last 3 months of the main 6-month randomized period), patients without any available assessment at endpoint Week 26 will be treated as failures (non-responders) in the analysis.

Similar rule to apply for FPG responders (defined by FPG ≤130 mg/dL (7.2 mmol/L) overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) hypoglycemia during the last 3 months of the main 6-month randomized period).

Handling of hypoglycemia event classification when some classification items are missing

Rule for handling missing data in classification items for hypoglycemia event will be provided in ADaM metadata.

Handling of missing data in the calculation of 8-point SMPG variables

For a given 8-point SMPG profile, at least 5 available measurements in the last 7 days are required to be taken into account in the statistical analyses (including the descriptive analyses at each time-point).

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

At least 3 pre-breakfast (fasting) 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).

Handling of missing data in the calculation of insulin doses

At each visit, the average daily insulin doses (basal, mealtime, and total) will be calculated as the average of the daily insulin doses available in the week (7 days) before the visit.

No minimum number of available doses will be required.

For insulin doses in U/kg, if the body weight measurement is missing at a given visit, the last available measurement from previous visit 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, plots, and statistical models).

No re-allocation will be performed for nominal visits already provided in the clinical database (Visit 1 to Visit 20).

SMPG

In the clinical database, SMPG profiles transferred from the e-diary will not be assigned to a protocol visit. For the analysis, they will be assigned to the next visit actually performed by the patient after the date/time of data collection (visit 3 to visit 20, or visit 700).

In the clinical database, SMPG assessments which do not correspond to an 8-point profile transferred from the e-diary will not be assigned to a protocol visit. For the analysis, they will be assigned to the next visit after the date/time of data collection (visit 2 to visit 20, or visit 700).

Insulin doses

In the clinical database, insulin doses transferred from the e-diary will not be assigned to a protocol visit. For the analysis, they will be assigned to the next on-site visit actually performed by the patient after the date/time of data collection.

End of treatment visit

The following analysis windows will be applicable to re-allocate the premature end of treatment assessments (premature EOT visit) for HbA1c and FPG assessments.

Table 2 - Analysis windows definition

Time point	Targeted study day	Analysis window in study days
WEEK 12	84	54 to 114
WEEK 26	182	152 to 212
WEEK 38	266	236 to 296
WEEK 52	364	334 to 394

Study days are calculated form the day of first IMP injection; the day of first IMP injection being Day1.

To retrieve all safety and AIA assessments performed at the end of treatment visit, the following process will be followed: 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.

Pharmacokinetic samples

The following analysis windows will be considered to select samples included in the PK analyses.

Basal insulin dosing regimen	Time point	Analysis time window
Morning	Pre-dose	within 1h before time of dosing
	4h post-dose	3h to 5h post dose
	8h post-dose	7h to 9h post-dose
Evening	12h post-dose	11h to 13h post-dose
	16h post-dose	15h to 17h post-dose
	20h post-dose	19h to 21h post-dose

2.5.5 Unscheduled visits

- The analysis windows mentioned in Section 2.5.4 will be applicable to re-allocate the unscheduled assessments (measurements from the central laboratory only) for HbA1c and FPG assessments.
- After applying the time windows as mentioned in Section 2.5.4, if two assessments are associated to the same time point, the closest from the targeted study day is used. In case of equality, the earliest measurement is used.

- The determination of baseline for HbA1c and FPG variables is based on all measurements from both scheduled and unscheduled visits (measurements from the central laboratory only). The determination of baseline for safety parameters is based on all assessments from both scheduled and unscheduled visits too. 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 (including results from local laboratory when no corresponding central laboratory results are available) 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

Not applicable.

This controlled open-label study will not to be terminated early with a positive claim for efficacy or safety.

The primary analysis of the efficacy and safety will be performed on the data collected during the main 6-month comparative treatment period. The timing of this analysis is when the last randomized patient has completed the main 6-month comparative treatment period.

The results of the primary analysis are not used to change the conduct of the ongoing study in any aspect.

The second analysis will be performed on all data collected during the 12-month study period.

4 DATABASE LOCK

It is planned to lock the database approximately 4 weeks after Last Patient Last Visit of the comparative treatment phase (6 months).

It is further planned to lock the database approximately 4 weeks after Last Patient Last Visit of the safety extension phase and the follow-up period. Software documentation

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

5 REFERENCES

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