NCT Number: NCT02735044

AMENDED CLINICAL TRIAL PROTOCOL 02

COMPOUND: HOE901

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

STUDY NUMBER: EFC13957

STUDY NAME: EDITION JUNIOR

VERSION DATE / STATUS: Approval date (23-Aug-2016) / Approved

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: HOE901-insulin glargine	**STUDY No: EFC13957** **STUDY NAME: EDITION JUNIOR**
TITLE	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
INVESTIGATOR/TRIAL LOCATION	Multinational, multicenter
PHASE OF DEVELOPMENT	3b
STUDY OBJECTIVES	**Primary objective** To compare the efficacy of a new formulation of insulin glargine (HOE901-U300) to Lantus in terms of change of glycated hemoglobin A1c (HbA1c) from baseline to endpoint (scheduled month 6) in children and adolescents with type 1 diabetes mellitus. **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 symptomatic 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 fasting plasma glucose (FPG) value (≤130 mg/dL [7.2 mmol/L]) at month 6 overall and without any episode of severe and/or documented symptomatic hypoglycemia during the last 3 months of the main 6-month randomized period; • Change in mean self-monitored plasma glucose (8-point SMPG profiles, 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.
STUDY DESIGN	Open-label, 1:1 randomized, active-controlled, 2-arm parallel-group, multicenter international study comparing HOE901-U300 versus Lantus in children and adolescents with Type 1 diabetes mellitus (T1DM). Randomization will be stratified by age group (<12 years and ≥12 years) and by HbA1c value (<8.5% and ≥8.5%), both at the screening visit. The study will include a 2-week screening period, a 6-month efficacy and safety period followed by a 6-month safety extension period and a 4-week post-treatment follow up period. Inclusion in the study is configured to ensure at least 30% of participants in the age range below 12 years.

STUDY POPULATION **Main selection criteria**	**Inclusion criteria** • Children and adolescents with T1DM for at least 1 year confirmed by typical symptoms at diagnosis and/or by antibody testing (presence of anti-GAD [glutamic acid decarboxylase] or anti-IA2 [islet antigen 2/tyrosine phosphatase] or anti-islet cell antibodies) and/or clinical features (eg, history of ketoacidosis); • Signed written informed consent obtained from parent(s)/legal guardian and written or oral assent obtained from patient. **Key exclusion criteria** • Age <6 years and ≥18 years at randomization; • Less than 1 year on insulin treatment prior to screening visit; • Less than 6 months on basal plus mealtime insulin and self-monitoring of blood glucose prior to screening visit; • Patients using pre-mix insulins in the last 3 months before screening visit or patients using human regular insulin as mealtime insulin in the last 3 months before screening visit; • Use of an insulin pump in the last 6 months before screening visit or plans to switch to pump within the next 6 months after screening visit; • No willingness to inject insulin glargine (Lantus or HOE901-U300) once daily; • HbA1c <7.5% or >11% at screening; • Initiation of any glucose-lowering medications in the last 3 months before screening visit; • Hospitalization or care in the emergency ward for diabetic ketoacidosis or history of severe hypoglycemia (as defined by need for glucagon or intravenous [IV] glucose) and accompanied by seizure and/or unconsciousness and/or coma in the last 3 months prior to screening visit; • Postmenarchal girls not protected by highly-effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy. Abstinence from sexual intercourse will be considered an acceptable form of birth control; • Pregnant or breast-feeding adolescents or adolescents who intend to become pregnant during the study period or who are at risk of getting pregnant due to any psychosocial reason during the study period.
Total expected number of patients	Approximately 450 patients will be randomized

STUDY TREATMENTS	
Investigational medicinal products **Formulation**	**Tested drug: HOE901-U300** HOE901-U300 will be supplied as a sterile, non-pyrogenic, clear, colorless solution in the Toujeo SoloStar prefilled (disposable) pen (insulin glargine 300 units/mL solution for subcutaneous injection). Each Toujeo SoloStar contains in total 450 units of insulin glargine (1.5 mL of 300 units/mL insulin glargine solution). This pen allows dose setting in the range of 1–80 units with minimum of 1 unit increment. Mixing of HOE901-U300 with other insulin products is not allowed nor dilution. **Control drug: Lantus (Insulin glargine)** Lantus will be supplied as a sterile, non-pyrogenic, clear, colorless solution in the marketed Lantus SoloStar prefilled (disposable) pen (insulin glargine 100 U/mL solution for subcutaneous injection). Each Lantus SoloStar contains in total 300 units of insulin glargine (3.0 mL of 100 units/mL insulin glargine solution). This pen allows dose setting in the range of 1–80 units with minimum of 1 unit increment. Mixing of Lantus with other insulin products is not allowed nor dilution.
Route of administration	**Tested drug:** HOE901-U300 will be administered by subcutaneous (SC) injections once daily (self-administration or administration assisted by the parent/caregiver). **Control drug**: Lantus will be administered by SC injections once daily (self-administration or administration assisted by the parent/caregiver).
Dose regimen	The same dose regimen will be used for HOE901-U300 and the comparator Lantus. Starting dose: The starting dose of the HOE901-U300 or Lantus will be the same (Unit for Unit) as the median dose (ie, the middle value out of the three values) of the total daily basal insulin doses in the last 3 days prior to the baseline visit, except if the patient was on more than once daily basal insulin products (eg, NPH insulin, insulin detemir), when the starting dose of HOE901-U300 or Lantus (U) should be reduced by approximately 20%. Dose titration: Dosing of insulin glargine given as HOE901-U300 or Lantus will be done based on self-measured, fasting, pre-breakfast plasma glucose levels (target range 90–130 mg/dL; 5.0–7.2 mmol/L) while avoiding hypoglycemia. After the end of study treatment patients on HOE901-U300 will have to switch from their daily HOE901-U300 dose to a non-study U100 basal insulin formulation by reducing the daily dose by 20% taking into account overall metabolic control.
Non-investigational medicinal product(s) **Formulation**	Patients in both treatment groups will continue with their fast-acting mealtime insulin analogue during the study. Solution for subcutaneous injection
Route of administration	Subcutaneous injection
Dose regimen	Dosing of the fast-acting mealtime insulin will be done based on self-measured, postprandial plasma glucose levels, target range for 2-hour post-prandial plasma glucose is <180 mg/dL (10.0 mmol/L) or, if clinically indicated, other individually determined goal.

ENDPOINTS	**Primary endpoint** HbA1c (change from baseline to endpoint [month 6/week 26]). **Secondary endpoints** • Percentage of patients with HbA1c values of <7.5% at month 6 overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) symptomatic 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 month 6 (central laboratory); • Percentage of patients with FPG ≤130 mg/dL (7.2 mmol/L) at month 6 overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) symptomatic 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 month 6; • Change in variability of 24-hour mean plasma glucose based on 8-point SMPG profiles from baseline to month 6; • Change in 8-point self-monitored plasma glucose (SMPG) profiles per time-point from baseline to month 6 (pre-prandial and 2 hour postprandial plasma glucose at breakfast, lunch and dinner, bedtime plasma glucose, nocturnal plasma glucose); **Safety** Hypoglycemia will be presented by hypoglycemia categories as defined in the publication American Diabetes Association (ADA) Workgroup on Hypoglycemia. In addition the composite category of severe and/or documented symptomatic hypoglycemia will be presented (documentation by SMPG <54 mg/dL; 3.0 mmol/L and SMPG ≤70 mg/dL; 3.9 mmol/L). Hyperglycemia (SMPG ≥252 mg/dL; 14 mmol/L) with ketosis (blood ketones ≥1.5 mmol/L) will be presented. All adverse events, serious adverse events and adverse events of special interest will be collected from the time of informed consent signature and then at each visit until the end of the study. Physical examination including Tanner puberty stage, vital signs, body weight, height, body mass index (BMI) and safety laboratory data. Anti-insulin antibodies (AIA).

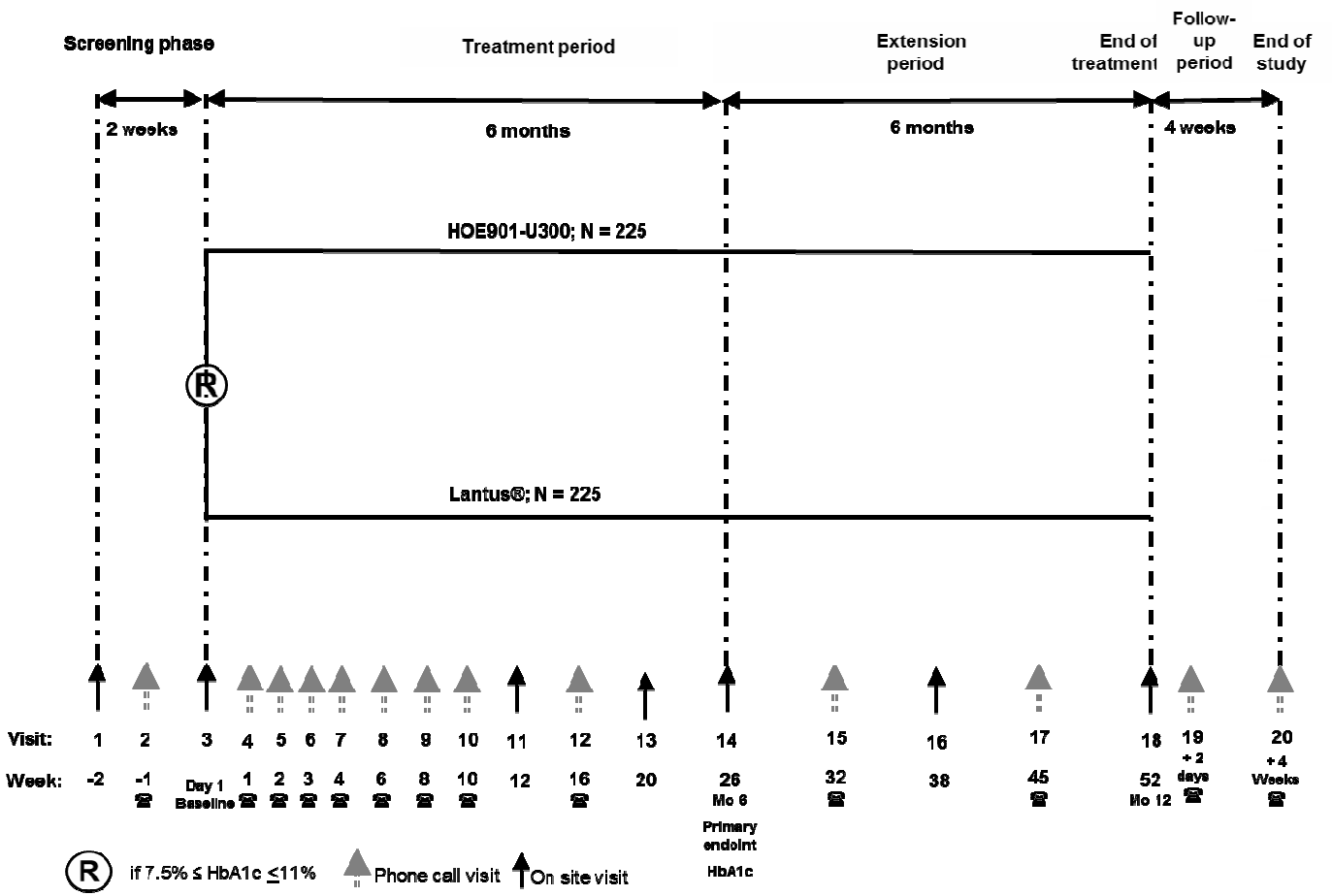
ASSESSMENT SCHEDULE	**Efficacy:** see Study Flowchart. **Safety:** see Study Flowchart. **Pharmacokinetics (PK):** Sparse sampling approach: 3 blood samples will be taken from all patients who consent to this assessment over a single day only after end of titration phase; during the period from Visit 13, Week 20 to Visit 14, Week 26 (see study flow chart). **Anti-Insulin Antibodies:** see study flow chart **Early termination:** In case of premature permanent Investigational Medicinal Product (IMP) discontinuation, all assessments normally planned for V18, Week 52 should be performed as soon as possible after last IMP administration. The 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. For safety considerations, patients who wish to terminate participation in the study whatsoever, at the minimum should be assessed using the procedure normally planned for the post-treatment follow-up 1 visit (Visit 19).
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size was chosen to ensure sufficient power for the primary endpoint (change in HbA1c from baseline to endpoint). 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% HbA1c 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. **General aspects of the analyses:** For efficacy analyses, the baseline is defined as the last available value obtained up to the date of randomization. **Analysis population:** The primary efficacy population is the intent-to-treat (ITT) population, which includes all randomized patients analyzed according to the treatment group allocated by randomization. The safety population is defined as all patients randomized and exposed to at least one dose of IMP, regardless of the amount of treatment administered. In the event of patients having received treatments that differed from those assigned according to the randomization schedule, then the safety analyses will be conducted according to the treatment received rather than according to the randomization groups. **Primary analysis:** The primary efficacy variable (change in HbA1c from baseline to endpoint [month 6]), will be analyzed in the ITT population, using all post-baseline data available on the main 6-month randomized period (ITT estimand). A multiple imputation approach in two parts 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 did not adhere to IMP but had the

	measurement for the primary endpoint. The adjusted least squares mean change in HbA1c from baseline to month 6 for each treatment group (HOE901-U300, Lantus) will be estimated, as well as the between-group (HOE901-U300, Lantus) difference and the 95% CI for the adjusted mean. A stepwise closed testing approach will be used for the primary efficacy variable to assess non-inferiority and superiority sequentially. Step 1 will proceed to assess non-inferiority of HOE901-U300 versus Lantus. To assess non-inferiority, the upper bound of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to endpoint between HOE901-U300 and Lantus will be compared with the predefined non-inferiority margin of 0.3% HbA1c. Non-inferiority will be demonstrated if the upper bound of the two-sided 95% CI of the difference between HOE901-U300 and Lantus on ITT population is <0.3%. Only if non-inferiority of HOE901-U300 versus Lantus has been demonstrated, step 2 will be performed to test superiority of HOE901-U300 over Lantus. The 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 endpoint between HOE901-U300 and Lantus on ITT population is <0 (zero). The tests for the primary endpoint (month 6) will be performed one-sided at level $\alpha = 0.025$. A sensitivity analysis will be performed on change in HbA1c from baseline to month 6 on patients who complete the main 6-month on-treatment period in the ITT population (ie, patients who perform Visit 14 [Week 26] and who do not permanently discontinue treatment). In order to assess the impact of missing data, a penalized multiple imputation (MI) and a tipping point analysis will also be performed as sensitivity analyses. **Analysis of secondary endpoints:** Categorical efficacy parameters (responder rates) 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. Secondary efficacy endpoints will be analyzed in the ITT population, using all available data on the 6-month randomized period (ITT estimand). A similar multiple imputation approach in two parts, as for the primary efficacy endpoint, will be used for change from baseline in FPG at Week 26. This analysis will be used descriptively. The other continuous secondary endpoints will be analyzed descriptively only. **PK analyses:** Blood samples will be collected to measure insulin glargine and its metabolites (M1 and M2) in plasma. PK analysis will be based on sparse sampling collected over a single day and will be done through a population PK approach. **Safety analyses:** Safety analyses will be descriptive using the safety population. Treatment emergent adverse events (TEAEs) are defined as AEs that developed or worsened or became serious during the period from the first dose administration of study treatment up to 2 days after the last administration.

	Hypoglycemia will be analyzed for: • Incidence of patients (%) with at least one hypoglycemia; • Hypoglycemia episodes per patient year exposure. Analysis will be done: • By time of the day: anytime of the day, nocturnal (00:00 to 05:59), daytime (06:00 to 23:59) and by hour of the day; • By treatment periods: 6-month TEAE period, 12-month TEAE period, from first injection of IMP to end of week 8, from start of week 9 to month 6, monthly rates; • Hypoglycemia by HbA1c and age range and by Tanner puberty stage; • Hypoglycemia by sleep status. Hyperglycemia (SMPG ≥252 mg/dL; 14 mmol/L) with ketosis (blood ketones ≥1.5 mmol/L) and AIA will be analyzed too.
DURATION OF STUDY PERIOD (per patient)	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, to evaluate insulin dose after switch-back from the IMP to a commercially available basal insulin. In total the study duration will be approximately 58 weeks per patient.
STUDY COMMITTEES	**Steering Committee:** ☐ Yes ☒ No **Safety Monitoring Committee:** ☐ Yes ☒ No Ongoing safety surveillance will be performed by a blinded endpoint assessment committee consisting of experts in pediatric diabetology and endocrinology. The committee will be provided on a regular basis with tabulated overviews of hypoglycemia events, TEAEs and serious TEAEs. Additionally, the committee will assess antigenicity data (AIA data and potential clinical correlates [hypersensitivity events, indicators of insulin resistance].

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1:1 randomization stratified by age group at screening (<12 years and ≥12 years) and by HbA1c (<8.5% and ≤8.5%) at screening

Visit schedule: From Visit 1 (week -2) to Visit 20 (week 52/EoT + 4 Weeks)

1.2 STUDY FLOW CHART

	Screening (2 weeks)		Treatment period (6 months)												Extension period (6 months)				Post treatment follow-up period (4 weeks)	
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18 [b] End of treatment	19 Post treat-ment/ Follow-up 1	20 Post treat-ment/ Follow-up 2
Visit window: Visit 3: ±3 days vs. V1 Visit 4 - 11: ±3 days vs. baseline Visit 12-18: ±5 days vs. baseline Visit 19: +2 days vs. V18 Visit 20: ±5 days vs. V18	Wk -2	Wk-1 ☎ [a]	Day 1 Base-line	Wk 1 ☎ [a]	Wk 2 ☎ [a]	Wk 3 ☎ [a]	Wk 4 ☎ [a]	Wk 6 ☎ [a]	Wk 8 ☎ [a]	Wk 10 ☎ [a]	Wk 12	Wk16 Mo 4 ☎ [a]	Wk 20	Wk 26 Mo 6	Wk 32 ☎ [a]	Wk 38	Wk 45 ☎ [a]	Wk 52 Mo 12	+ 48 hours ☎ [a]	+ 4 weeks ☎ [a]
Informed consent	X																			
Inclusion/Exclusion criteria	X	X	X																	
Medical and surgical history, demography, diabetes history, prior medication history	X																			
Physical examination [c]	X		X											X				X		
Vital signs [d]	X		X								X		X	X		X		X		
Body weight, height [e]	X [e]		X								X [e]			X [e]		X [e]		X [e]		
Tanner puberty stage [f]			X											X				X		
Dispensation of glucose meter, blood ketone meter & diary (and training at V1, V3 as needed and dispensation of corresponding supplies whenever needed)	X																			
Dispensation of urine container & training	X																			
Training on SMPG profiles, hypoglycemia (as needed)	X		X								X		X	X		X				
Diet and lifestyle counseling (as needed)	X		X								X		X	X		X		X		
Dispensation of study medication (and training at V3)			X								X		X	X		X				
Counting / collecting used and unused pens											X		X	X		X		X		

	Screening (2 weeks)		Treatment period (6 months)												Extension period (6 months)				Post treatment follow-up period (4 weeks)	
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18 [b] End of treatment	19 Post treat-ment/ Follow-up 1	20 Post treat-ment/ Follow-up 2
Visit window: Visit 3: ±3 days vs. V1 Visit 4 - 11: ±3 days vs. baseline Visit 12-18: ±5 days vs. baseline Visit 19: +2 days vs. V18 Visit 20: ±5 days vs. V18	Wk -2	Wk-1 ☎ [a]	Day 1 Base-line	Wk 1 ☎ [a]	Wk 2 ☎ [a]	Wk 3 ☎ [a]	Wk 4 ☎ [a]	Wk 6 ☎ [a]	Wk 8 ☎ [a]	Wk 10 ☎ [a]	Wk 12	Wk16 Mo 4 ☎ [a]	Wk 20	Wk 26 Mo 6	Wk 32 ☎ [a]	Wk 38	Wk 45 ☎ [a]	Wk 52 Mo 12	+ 48 hours ☎ [a]	+ 4 weeks ☎ [a]
Compliance Check (use of IMP and NIMP; glucose meter, ketone meter, diary, review of SMPG)			X								X		X	X		X		X		
Review of diary data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IVRS/IWRS contact	X [g]		X								X		X	X		X		X		
Randomization			X																	
Documentation and review of basal, prandial and corrective fast-acting insulin doses	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-monitoring of plasma glucose [h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-monitoring of blood ketones [i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Central Laboratory																				
HbA1c	X		X								X			X		X		X		
Fasting Plasma Glucose (FPG)			X											X				X		
C-peptide (fasting)			X																	
Safety Laboratory																				
Hematology [j], Clinical Chemistry [k]	X													X				X		
Anti-insulin antibody			X								X			X				X		
Hepatitis Serology [l]	X																			
Urine analysis [m]	X																	X		
Microalbuminuria and albumin/creatinine ratio [n]			X																	

	Screening (2 weeks)		Treatment period (6 months)												Extension period (6 months)				Post treatment follow-up period (4 weeks)	
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18 [b] End of treatment	19 Post treat-ment/ Follow-up 1	20 Post treat-ment/ Follow-up 2
Visit window: Visit 3: ±3 days vs. V1 Visit 4 - 11: ±3 days vs. baseline Visit 12-18: ±5 days vs. baseline Visit 19: +2 days vs. V18 Visit 20: ±5 days vs. V18	Wk -2	Wk-1 ☎ [a]	Day 1 Base-line	Wk 1 ☎ [a]	Wk 2 ☎ [a]	Wk 3 ☎ [a]	Wk 4 ☎ [a]	Wk 6 ☎ [a]	Wk 8 ☎ [a]	Wk 10 ☎ [a]	Wk 12	Wk16 Mo 4 ☎ [a]	Wk 20	Wk 26 Mo 6	Wk 32 ☎ [a]	Wk 38	Wk 45 ☎ [a]	Wk 52 Mo 12	+ 48 hours ☎ [a]	+ 4 weeks ☎ [a]
Pregnancy test (post menarchal girls) [o]; review of contraceptive measures	X		X								X		X	X		X		X		
Admission for PK sparse sampling [p]													X							
Insulin dose after switch-back (basal and fast-acting)																			X	X
Collection of diary and, if mandatory by local regulations, glucose meter & blood ketone meter																				X [q]
AE / SAE	To be assessed and reported (if any) throughout the study (report SAE to the sponsor within 24 hours)																		X	X
Injection site reactions, hypersensitivity reactions	To be assessed and reported (if any) throughout the study																		X	X
Hypoglycemia recording	To be assessed and reported (if any) throughout the study																		X	X

a) ☎ Mandatory telephone visit or optional clinical visit. Additional, optional telephone visits to monitor and support the progress of insulin titration will be scheduled at the discretion of the investigator

b) Or early termination visit. In case of premature and permanent IMP discontinuation, all assessments planned for V18 should be performed as soon as possible after last study treatment administration. The patient will be asked to attend all scheduled study visits and undergo study procedures until the planned end of treatment visit (or end of the 4-week post-treatment follow up period, whichever comes last). A post-treatment follow-up 1 safety phone call should be planned 2 days (+2 days) after IMP discontinuation as well as post-treatment follow-up 2 safety phone call 4 weeks (±5 days) after IMP discontinuation

c) The date of menarche will be captured if applicable

d) At each on-site visit: Heart rate, blood pressure in sitting position

e) Height at visits week -2 (screening), week 12, week 26 and during the extension period at visit week 38 and week 52 (or early IMP termination). BMI will be determined based on body weight and height.

f) Tanner puberty stage until complete sexual maturity defined by Tanner stage 5

g) IVRS/IWRS contact: before any blood sample is drawn because the patient number as allocated by IVRS/IWRS has to be reported on the laboratory requisition forms

h) Self-monitored plasma glucose:

Fasting plasma glucose: on at least 5 days in the week before each visit;

It is recommended to perform fasting SMPG daily throughout the study. When up-titration of the IMP has been completed and fasting (pre-breakfast) SMPG is stable in the target range, the number of fasting SMPG checks can be reduced according to the investigator's judgment, however at least 3 fasting (pre-breakfast) SMPG measurements per week should be done. On days when 8-point profiles are done, fasting SMPG will be considered as the second point of measurement, ie, the before breakfast time point.

8-point blood glucose profiles (starting with a measurement between 01:00 – 04:00 AM at night; before and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner; at bedtime): on at least one day in the week before the baseline visit, and the visits week 26 and week 52. Special attention should be paid that the nighttime SMPG value is recorded (1)

SMPG during symptomatic hypoglycemia: whenever the patients feel hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible. Patients should be instructed to measure plasma glucose levels prior to the administration of glucose or carbohydrate intake whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation. Details of all hypoglycemia events will be reported on dedicated electronic Case Report Form (e-CRF) pages.

Complementary SMPG: it is recommended to perform 4-6 SMPG daily at different times of the day and measure the nighttime SMPG once weekly for optimal control of glycemia and adjustment of the insulin regimen. Additional SMPG are recommended in association with exercise/sport (before start, during and after activity and at bedtime) and at sick days, menses.

Tests using the control solution: It is recommended to perform tests with the control solution before first use of the study glucose meter, in cases when SMPG reading is considered incorrect or inconsistent with symptoms and whenever a new batch of test strips is used.

i) Anytime SMPG ≥252 mg/dL (14 mmol/L) is measured in an unwell child or when persistent blood glucose values above ≥252 mg/dL (14 mmol/L) without substantial decline are present over a period of approximately 60-120 min after an extra dose of rapid-acting insulin, or during illness with fever and/or vomiting. Ketone readings are to be documented in the diary.

j) Hematology: Erythrocytes, hemoglobin, hematocrit, leukocytes, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets

k) Clinical chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine, estimated glomerular filtration rate (eGFR) (Schwartz equation), sodium, potassium, chloride, calcium

l) Hepatitis serology: Hepatitis B surface antigen (HbsAg) and Hepatitis C viral antibodies (HCAb); if HCAb positive: reflex test for Hepatitis C virus (HCV) RNA

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

n) Microalbuminuria, albumin/creatinine ratio: in first morning urine sample. Container to be dispensed at Visit 1

o) For post-menarchal girls; serum pregnancy test for screening (central laboratory); urine pregnancy test (at study site) for subsequent monitoring; review of contraceptive measures at each on-site visit

p) PK sparse sampling will be collected in patients who provided dedicated consent over one day after the end of titration phase during the period from visit 13, week 20 to visit 14, week 26. The sample times will depend on the existing dosing regimen:

- Participants with dose administered in the evening (~ 20:00) on the day before the date of the visit: sample schedule: 12 h, 16 h and 20 h post-dose (which will be around 08:00, 12:00, 16:00 on day of visit)
- Participants with dose administered in the morning (~ 08:00) on the day of the visit: sample schedule: pre-dose, 4 h, and 8 h post-dose (which will be around 08:00, 12:00, 16:00 on visit day)

q) At last study visit (if performed as an on-site visit) or shortly thereafter

Note: Telephone counseling will be available at any time as needed.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

ADA:	American Diabetes Association
AESI:	adverse event of special interest
AIA:	anti-insulin antibodies
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BMI:	body mass index
CI:	confidence interval
CRF:	case report form
CSR:	clinical study report
DBP:	diastolic blood pressure
DKA:	diabetic ketoacidosis
DRF:	discrepancy resolution form
ECG:	electocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
GCP:	good clinical practrice
HbA1c:	glycated hemoglobin A1c
HBsAg:	hepatitis B surface antigen
HCAb:	hepatitis C viral antibodies
HCV:	hepatitis C virus
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
ICH:	International Conference on Harmonization
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
ITT:	intent-to-treat
IV:	intravenous
IVRS:	interactive voice response system
IWRS:	interactive web response system
MI:	multiple imputation
NGSP:	national glycohemoglobin standardization program
NIMP:	non-investigational medicinal product
PCSA:	potentiallly clinically significant abnormality
PD:	pharmacodynamics
PK:	pharmacokinetics
PT:	preferred term
SBP:	systolic blood pressure

SC.:	subcutaneous
SE:	standard error
SMPG:	self-measured plasma glucose
SOC:	system organ class
T1DM:	type 1 Diabetes Mellitus
T2DM:	type 2 Diabetes Mellitus
TEAE:	treatment emergent adverse event
ULN:	upper limit of normal range

4 INTRODUCTION AND RATIONALE

Insulin glargine U100 (HOE901) is 21^{A}-Glycine-30^{B}a -L-arginine-30^{B}b-L-Arginine-human insulin, a recombinant analog of human insulin providing a 24-hour basal insulin supply after a single-dose subcutaneous (SC) injection. Insulin glargine U100 has been marketed as Lantus® for approximately 15 years. Its efficacy and safety are well-known through extensive data collection involving over 200 000 patients in clinical studies, including randomized, controlled clinical trials and the results of postmarketing surveillance arising from approximately 66.9 million patient-years of clinical experience. Further information on Lantus, including important clinical trials performed pre- and postregistration, can be found in the national product label or in the Product Information (2) and Investigator´s Brochure HOE901 (3).

Insulin glargine U100 (Lantus) is approved for a once daily injection for the treatment of diabetes in adults and pediatric (age range 6 to 15 years; in the EU also in preschoolers 1–6 years of age) patients with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM).

HOE901-U300 is a new formulation of insulin glargine. It has the same composition as the marketed insulin glargine 100 U/mL formulation with adjustment of 3-times the amount of Active Pharmaceutical Ingredient (API) and corresponding Zinc content. Toujeo was approved in the US on February 25, 2015 and in the European Union on April 12, 2015 for the treatment of adults with diabetes mellitus. Review of the regulatory submission documents is ongoing in other countries worldwide.

Insulin glargine has the same metabolism regardless of the concentration of the formulation, notably the formation of 21^{A}-Gly-human insulin (M1 metabolite) as the predominant circulating metabolite. The difference between HOE901-U300 and Lantus rests in the pharmacokinetics/pharmacodynamics (PK/PD) profile which shows slower and more prolonged absorption of HOE901-U300 resulting in a flatter time-concentration profile.

Based on the results of Phase 1 studies with HOE901-U300 in healthy subjects and adults with T1DM (PKD10086, PKD11627 and TDR11626), it was anticipated that compared to Lantus, the prolonged and flatter profile of the glucose-lowering activity of HOE901-U300 (up to 36 hours) could result in more constant glycemic control within a 24-hour injection interval, in turn, resulting in less circadian fluctuation in blood glucose levels and lower risk of hypoglycemia.

In Phase 3 clinical studies in a broad range of adult patient population with T1DM and T2DM, HOE901-U300 has shown comparable efficacy, safety and tolerability to Lantus with different pre-treatment regimens and dose requirements of insulin. In patients with T2DM, HOE901-U300 was consistently associated with a lower risk of hypoglycemia as compared with Lantus, as shown for severe and/or confirmed hypoglycemia. In the study in T1DM (EFC12456) there was no difference between the treatment groups for percentages of patients reporting hypoglycemia or the event rates per patient year. In the study the assessment of the hypoglycemia risk associated with the basal insulin may have been confounded by the concomitant use of fast-acting insulin.

Further details on HOE901-U300 can be found in the Investigator's Brochure HOE901.

Since Lantus is approved in the T1DM pediatric population 6 to 18 years of age, it is anticipated that HOE901-U300 may also be used in this population. This study is planned to generate evidence of efficacy and safety of HOE901-U300 in children and adolescents 6-17 years of age with T1DM requiring insulin treatment.

The purpose of this multicenter, randomized, open-label, 2-arm parallel-group study in children and adolescents is to compare the efficacy and safety of HOE901-U300 with that of Lantus, both given once-daily by SC injection. Patients with type 1 diabetes and glycated hemoglobin A1c (HbA1c) in the range of 7.5% to 11% on a basal plus fast-acting insulin regimen are eligible for the study. Patients with hospitalization for diabetic ketoacidosis (DKA) or history of severe hypoglycemia (as defined by need for glucagon or intravenous [IV] glucose) during the previous 3 months, are excluded from the study.

Patients will be randomized (1:1) to receive HOE901-U300 or Lantus.

Patients will be stratified by their HbA1c (<8.5%; ≥8.5%) and age group (<12 years; ≥12 years) at the time of screening. Inclusion in the study is configured to ensure at least 30% of participants in the age range below 12 years. The primary efficacy analysis will test non-inferiority of HOE901-U300 compared to Lantus in terms of change of HbA1c from baseline to endpoint (month 6; non-inferiority margin 0.3% HbA1c units).

Secondary analyses will be performed to evaluate the effects of the flat insulin profile over at least 24 hours, which should result in more sustained glycemic control within predefined blood glucose margins. The analyses will be based on fasting plasma glucose (FPG, central laboratory), on self-monitored plasma glucose measurements (SMPG; eg, 8-point glucose profiles), hypoglycemia reports and insulin doses.

A thorough hypoglycemia analysis will be performed. Evaluations will include incidence of hypoglycemia (number of patients with at least one hypoglycemia) and hypoglycemia episodes per patient year. Hypoglycemia episodes will be evaluated overall and by time of the day, (ie, daytime, nocturnal, overall, distribution over the 24-hour period) and by study periods. The American Diabetes Association (ADA) definitions will be applied to define the hypoglycemia categories (4, 5). All confirmed hypoglycemia categories will be also evaluated for the more stringent SMPG threshold of <54 mg/dL (3.0 mmol/L). In addition, composite categories including the clinically important categories of severe hypoglycemia and/or symptomatic hypoglycemia documented by SMPG <54 mg/dL (3.0 mmol/L) and ≤70 mg/dL (3.9 mmol/L) will be evaluated. Other safety evaluation will include the comparison of clinical treatment emergent adverse events (TEAEs), hyperglycemia with ketosis, hypersensitivity reactions and injection site reactions. Laboratory safety will include the standard hematology and biochemistry and the determination of anti-insulin antibodies (AIA) and assessments of effects on weight.

PK of insulin glargine 100 U/mL and metabolites were evaluated in adults (study TDR11626) and in children 1–6 years of age (EFC11202, PRESCHOOL) with T1DM. The principal pharmacologically active entity in serum was the insulin glargine metabolite M1 in both populations. Insulin glargine parent compound and metabolite M2 C_{trough} were below limit of quantification (<0.2 ng/mL) in the vast majority of patients. No PK data exists on insulin glargine HOE901-U300 in pediatrics and adolescents 6 to 18 years of age. In this study, serum concentration of insulin glargine and its metabolites M1 and M2 will be determined at various

time points over a single day according to a defined sparse sampling scheme to evaluate the time course of accumulation and the metabolism of insulin glargine given as HOE901-U300 or Lantus. The blood samples will be taken after the end of titration phase, during the period from visit 13, week 20 to visit 14, week 26) from all participants who provided consent for PK data collection.

The study consists of a 2-week screening period and a treatment period of 6 months, followed by a comparative on-treatment 6-month safety extension period and a 4-week post-treatment follow-up period.

HOE901-U300 or Lantus will be injected subcutaneously once daily, either in the morning or in the evening. Efforts will be made to maintain the same dosing time (hh:mm) during the whole treatment period so that the interval between once daily injections of the investigational medicinal product (IMP) will be kept at or close to 24 hours. Patients will continue with their mealtime fast-acting insulin analogue.

During the 6-month treatment period the basal insulin dose will be titrated using a titration schedule to reach the target fasting/pre-prandial plasma glucose in the range of 90 to 130 mg/dL (5.0 to 7.2 mmol/L), bedtime / nocturnal plasma glucose in the target range of 90–150 mg/dL (5.0 and 8.3 mmol/L) (6), avoiding hypoglycemia. Mealtime insulin will be adjusted to achieve a target 2-hour postprandial plasma glucose <180 mg/dL (10.0 mmol/L). After reaching the target range, the insulin dose will be adjusted depending on the prevailing plasma glucose to maintain the glycemic control over the remaining study duration. Patients will be encouraged to measure and record frequent SMPG values on a daily basis at different times of the day and in line with recommendations by the International Society for Pediatric and Adolescent Diabetes (ISPAD) (1). Patients will be instructed to measure and record their blood ketones if SMPG is ≥252 mg/dL (≥14 mmol/L) while being unwell (eg, feeling sick or nauseated) or when persistent blood glucose values ≥252 mg/dL (14 mmol/L) without substantial decline are present over a period of approximately 60-120 min after an extra dose of rapid-acting insulin analogue, or during illness with fever and/or vomiting. Ketone readings 1.5 mmol/L or more and concomitant SMPG ≥252 mg/dL (14 mmol/L) will be considered as alert for development of diabetic ketoacidosis and the investigator will be contacted immediately. Patients who have completed the 6-month treatment period will continue their study treatment during the 6-month comparative safety extension period to evaluate long-term safety and maintenance of efficacy.

After end of study treatment (Month 12) patients will be monitored after switch-back to commercial basal insulin during the 4-week post-treatment follow up period. Patients who prematurely and permanently discontinue study treatment will be asked to continue attending study visits and undergo assessments according to the schedule until the planned end of study treatment (Month 12). For patients who prematurely and permanently discontinue study treatment during the main 6-month treatment period, as a minimum visit at Week 26/Visit 14 (assessments of primary and secondary efficacy endpoints) should be conducted.

The number of visits to the study site (7 out of 20 visits planned) is kept at a minimum in order to minimize the impact on the daily activities of the adolescents and their caregivers. Instead, monitoring of glycemic control including self-monitored plasma glucose, hypoglycemia events, titration of the basal insulin, dosing of study and mealtime insulin is done during phone-call visits. If deemed necessary by the investigator or by the patient/caregiver, on-site visits may be arranged any time.

The overall benefit-risk assessment does not raise any concern for this study, because there is no reason to suppose that HOE901-U300 would pose a greater risk or confer worse efficacy outcomes than in the adult population or than Lantus in the population consisting of children and adolescents with T1DM. In this study, HOE901-U300 will be administered using the Toujeo SoloStar® prefilled (disposable) pen. Its accuracy has been determined to be in accordance with respective standards. The safety of patients in this study, including hypoglycemia events, will be closely followed within the framework of clinical trial.

5 STUDY OBJECTIVES

5.1 PRIMARY

To compare the efficacy 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 with type 1 diabetes mellitus.

5.2 SECONDARY

- 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 symptomatic 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 symptomatic hypoglycemia during the last 3 months of the main 6-month randomized period;
  - Change in mean self-monitored plasma glucose (8-point SMPG profiles, 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.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

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.

PK sparse sampling: all participants who will give assent (and will have additional dedicated consent form signed by their parent) will provide 3 blood samples over a single day in the period between Visit 13 (week 20) and Visit 14 (week 26), inclusive, see Section 9.3.1.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

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).

6.2.2 Determination of end of clinical trial (all patients)

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

6.3 INTERIM ANALYSIS

No interim analysis is planned.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Children and adolescents with T1DM for at least 1 year confirmed by typical symptoms at diagnosis and/or by antibody testing (presence of anti-GAD [glutamic acid decarboxylase] or anti-IA2 [islet antigen 2/tyrosine phosphatase] or anti-islet cell antibodies) and/or clinical features (eg, history of ketoacidosis);

I 02. Signed written informed consent obtained from parent(s)/legal guardian[1] (hereinafter the "parent") and written or oral assent obtained from patient.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 3 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Age <6 and ≥18 years at randomization;

E 02. Less than 1 year on insulin treatment prior to screening visit;

E 03. Less than 6 months on basal plus mealtime insulin and self-monitoring of blood glucose prior to screening visit;

E 04. Patients using pre-mix insulins in the last 3 months before screening visit or patients using human regular insulin as mealtime insulin in the last 3 months before screening visit;

E 05. Use of an insulin pump in the last 6 months before screening visit or plans to switch to pump within the next 6 months after screening visit;

E 06. Any contraindication to use of insulin glargine as defined in the national product label;

E 07. No willingness to inject insulin glargine (Lantus or HOE901-U300) once daily;

E 08. HbA1c <7.5% or >11% at screening;

[1] "Legal guardian" means an individual or judicial or other body authorised under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research. In this document "parent" will be used as a synonym for "legal guardian"

E 09. Hospitalization or care in the emergency ward for diabetic ketoacidosis or history of severe hypoglycemia (as defined by need for glucagon or IV glucose) and accompanied by seizure and/or unconsciousness and/or coma in the last 3 months prior to screening visit;

E 10. Initiation of any glucose-lowering agents in the last 3 months before screening visit;

E 11. End stage renal disease (creatinine clearance <15 mL/min/1.73m^2 or on renal replacement treatment);

E 12. Hemoglobinopathy or hemolytic anemia, transfusion of blood or plasma products within 3 months prior to screening visit;

E 13. History of drug or alcohol abuse within 6 months prior to the time of screening;

E 14. Patients with severe or unstable, clinically relevant non-diabetes disorders making implementation of the study protocol or interpretation of the results of the study difficult or patients with short life expectancy or any other medical condition that might interfere with the evaluation of study medication according to investigator's medical judgment;

E 15. Active liver disease or alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >3 times upper limit of normal or total bilirubin >1.5 times upper limit of normal (except in case of documented Gilbert's syndrome) at screening;

E 16. Positive test for hepatitis B surface antigen and/or infection with hepatitis C virus at screening;

E 17. Use of investigational drug(s) within 1 month or 5 half-lives, whichever is longer prior to the screening visit;

E 18. Use of systemic glucocorticoids (excluding topical application or inhaled forms) for one week or more within 3 months prior to the time of screening;

E 19. Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol;

E 20. Mental condition rendering the patient or parent unable to understand the nature, scope and possible consequences of the study, including blood glucose monitoring requirements including the documentation of SMPG data and insulin dosing, evidence of an uncooperative attitude and/or inability to return for follow-up visits, and unlikely to complete the study;

E 21. Parents/patients not willing to undergo all study assessments and treatments, including home blood glucose monitoring, multiple daily insulin injections, and visits, as dictated by the protocol (if a telephone is not available patients may undergo all visits in person);

E 22. Patients/parents not willing to be treated with basal/bolus insulin therapy for the duration of the study. Patients/parents must be willing to use a single injection of insulin glargine as their sole basal insulin during the study as assigned by the randomization process. They

must agree to use rapid acting insulin as their bolus insulin for the duration of study treatment;

E 23. Adolescents who will reach the legal age of maturity during the study period if continuity of care at the study site cannot be ensured due to transition from pediatric to adult health care;

E 24. Parent unable to read and write;

E 25. Parent is related to or an employee of sanofi or sponsor representatives or member of the investigator's staff;

E 26. Postmenarchal girls not protected by highly-effective method(s) of birth control (as defined in Appendix B) and/or who are unwilling or unable to be tested for pregnancy. Abstinence from sexual intercourse will be considered an acceptable form of birth control;

E 27. Pregnant or breast-feeding adolescents or adolescents who intend to become pregnant during the study period or who are at risk of getting pregnant due to any psychosocial reason during the study period.

7.2.2 Exclusion criteria related to the current knowledge of Sanofi compound

E 28. History of hypersensitivity to metacresol or other excipient of Lantus or HOE901-U300.

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

E 29. Patients or parents who withdraw consent during the screening period (patient who is not willing to continue or fails to return).

E 30. Patients/parents who cannot demonstrate the proper use of injection pens, diary or glucose meter before randomization or who were not compliant to the fasting SMPG measurement schedule.

A patient must not be randomized more than once. Patients can be re-screened one time before randomization in case of non-evaluable exclusion criteria or in cases where original screen failure was due to reasons expected to change at rescreening and based upon the investigator's clinical judgment. New informed consent has to be signed by the parent before re-screening (and new assent obtained from the patient).

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

The IMP is insulin glargine. It will be provided either as HOE901-U300 (tested drug) or as Lantus (control drug).

8.1.1 Formulations

Tested drug: HOE901-U300

HOE901-U300 will be supplied as a sterile, non-pyrogenic, clear, colorless solution in the Toujeo SoloStar prefilled (disposable) pen (insulin glargine 300 units/mL solution for subcutaneous injection).

Each Toujeo SoloStar contains in total 450 units of insulin glargine (1.5 mL of 300 units/mL insulin glargine solution). This pen allows dose setting in the range of 1 – 80 units with minimum of 1 unit increment.

Mixing of HOE901-U300 with other insulins is not allowed nor dilution.

Control drug: Lantus (Insulin glargine)

Lantus will be supplied as a sterile, non-pyrogenic, clear, colorless solution in the marketed Lantus SoloStar prefilled (disposable) pen (insulin glargine 100 U/mL solution for subcutaneous injection).

Each Lantus SoloStar contains in total 300 units of insulin glargine (3.0 mL of 100 units/mL insulin glargine solution). This pen allows dose setting in the range of 1 – 80 units with minimum of 1 unit increment.

Mixing of Lantus with other insulins is not allowed nor dilution.

8.1.2 Injection devices and training for injection devices

8.1.2.1 Injection devices

Disposable injection devices (prefilled study drug pens) with needles are provided to each patient for the injection of HOE901-U300 or Lantus specifically labeled for use in the study.

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

- BD Ultra Fine Needles 32 G x 4 mm
- BD Ultra Fine Needles 31 G x 5 mm

If deemed appropriate by the investigator, other types of needles approved for use with the SoloStar pen may be used.

Handling procedures of the disposable pen and needles and administration technique is provided in specific manuals (see Pen leaflet). The patients (and/or parents) are trained on the use of the study drug disposable pen and needles by the study staff and provided with an instruction leaflet at Visit 3. For the duration of the treatment, the participants will be required to use the same type of study drug disposable pens and needles.

Pen-device issues (malfunctions) associated with the IMP pen that are not resolved by further guidance/review of instructions or troubleshooting with the pen during the visit (on site visit or phone visit), must be reported to the sponsor by means of a product technical complaint (PTC) form. (This procedure is described in a separate manual.) The pen associated with the event should be retrieved and sent together with the form to the manufacturing site for technical investigation.

Injection pens should never be shared with others.

8.1.2.1.1 Injection pen for HOE901-U300

Patients randomized to HOE901-U300 will be supplied with the appropriate number of disposable pens for insulin glargine 300 U/mL and needles according to the dose range.

Each pen contains a cartridge with a total 450 units of insulin glargine. Doses can be set in steps of 1 unit. If a dose of HOE901-U300 greater than 80 units is required, it will be given as two or more consecutive SC (subcutaneous) injections at the same time with the daily dose split in equal or close to equal doses. Splitting the doses into a morning and evening injection is not allowed.

8.1.2.1.2 Injection pen for Lantus

Patients randomized to Lantus will be supplied with the appropriate number of disposable pens for insulin glargine 100 U/mL and needles according to the dose range.

Each pen contains a cartridge with a total 300 units of insulin glargine. Doses can be set in steps of 1 unit. If a dose of Lantus greater than 80 units is required, it will be given as two or more consecutive SC injections at the same time with the daily dose split in equal or close to equal doses. Splitting the doses into a morning and evening injection is not allowed.

8.1.3 Dosage schedule

The study medication, HOE901-U300 or Lantus, will be injected by deep subcutaneous injection (either self-administered or injected by the parent) in any of the following areas: buttocks, thighs, abdomen, or upper arms. Changes to another area of injection will be done periodically and will be consistent with the habits of the individual patient. Injection sites (ie, the very place of injection within the area of injection) will be rotated within that area from injection to injection (what may include rotating the sides [left, right] of the body) to reduce the risk of injection site reactions. The injection areas for IMP and non-investigational medicinal product (NIMP) should

be different so that any injection site reactions can be attributed specifically either to IMP (HOE901-U300 or Lantus) or NIMP (fast-acting insulin analogue). Injection site reactions associated with administration of the IMP or NIMP, if any, will be reported as Adverse Events (see Section 10.4.1 and Section 10.6.3) and information on localization and insulin (IMP or NIMP) is required.

The IMP will be administered once daily either in the morning or in the evening. It is expected that patients taking their pre-study basal insulin once daily in the morning will continue with the morning regimen of the IMP during the study as well as patients taking their pre-study basal insulin once daily in the evening will continue with the evening regimen. At Visit 3 (baseline) patients receiving more than 1 daily injection of basal insulin will change to once daily injection either in the morning or in the evening, at the discretion of the patient/parent/investigator. Once fixed at randomization, the time of day of injection with the IMP (ie, either in the morning or in the evening) will remain the same throughout the whole study treatment duration. Efforts will be made to maintain the same dosing time (hh:mm) during the whole treatment period so that the interval between once daily injections of the IMP will be kept at or close to 24 hours. Patients will continue with their mealtime fast-acting insulin analogue which is not to be changed during the study (see Section 8.2).

8.1.4 Starting dose

The median (ie, the middle value out of the three values) of the total daily basal insulin doses in the last 3 days prior to the baseline visit will be used for the calculation of the starting dose. With the exception of those on more than once daily basal insulin products (eg, NPH insulin, insulin detemir), patients will switch 1:1 (Unit for Unit) from their daily basal insulin dose to HOE901-U300 or Lantus. In patients who switch from more than once daily basal insulin products, the starting dose of HOE901-U300 or Lantus (U) should be reduced by approximately 20%. If deemed necessary by the investigator the first dose of the IMP may be administered at a reduced dose. See also Section 10.1.2.1

8.1.5 Dose adjustment

Doses of HOE901-U300 and Lantus will be titrated to achieve glycemic targets of fasting SMPG without hypoglycemia.

The same dosing schedule will be applied for Lantus and HOE901-U300. Changes in the Lantus or HOE901-U300 dose are based on fasting SMPG measurements using the glucometer provided for this study according to the following schedule (Table 1). Other pre-prandial (pre-lunch, pre-dinner) SMPG measurements will be taken into account, too.

The recommended target range for fasting, pre-prandial plasma glucose is 90 to 130 mg/dL (5.0 to 7.2 mmol/L).

Table 1 - IMP dose titration schedule

Median* fasting (pre-breakfast) SMPG	Current basal insulin dose	Dose adjustment of HOE901-U300 or Lantus
Above target range: • >180 mg/dL (10.0 mmol/L) and no evidence of severe hypoglycemia	<15 U/day	+ 2 U
	≥15 U/day	+ 4 U
Above target range: • >130 to 180 mg/dL (7.2 mmol/L to 10.0 mmol/L) and no evidence of severe hypoglycemia	<15 U/day	+ 1 U
	≥15 U/day	+ 2 U
In target range: • 90 to 130 mg/dL (5.0 to 7.2 mmol/L) and no evidence of severe hypoglycemia		No change of basal insulin dose
Below target range: • <90 mg/dL (5.0 mmol/L)	<15 U/day	- 1 U
	≥15 U/day	- 2 U
In case of hypoglycemia:		Doses may be reduced at any time
In case relevant hypoglycemia is reported (without adequate explanation, eg unexpected exercise)	<15 U/day	- 1 U
	≥15 U/day	- 2 U
In case of **severe hypoglycemia** (neurological symptoms, 3rd party assistance required)		In addition to dose reduction, upward titration may be stopped for 1 week.

* Median = the middle value of fasting (pre-breakfast) SMPG out of the three values from last 3 days including the current day

Good clinical judgment is to be exercised while titrating the basal insulin dose. Adjustment of the basal insulin dose should be done once per week.

When implementing the insulin titration dose, a dose increase may be split into 2 incremental dose steps every 3-4 days, rather than implementing the entire dose increase at one time, if it was concluded by the investigator or medically qualified designee to be in the best interest of the patient to do so. Dose titration should be done no more frequently than every 3-4 days.

The dose of Lantus or HOE901-U300 will be increased until the patient reaches the target fasting SMPG. Best efforts should be made to complete up-titration of either basal insulin by 6 to 12 weeks. Thereafter, until the end of the study, the dose will be adjusted as necessary to maintain the glycemic control.

It is recommended to attain and maintain bedtime and nocturnal plasma glucose in the target range of 90 to 150 mg/dL (5.0 to 8.3 mmol/L), avoiding hypoglycemia.

If needed, additional unscheduled contacts (phone, on-site visit) should be made available for patients/parents to discuss dose adjustments in-between the scheduled visits already outlined in the protocol.

Additionally, adherence to the titration rules will be monitored by the sponsor. Non-compliance to the titration schedule will be raised to the attention of the investigator for explanation or correction. If applicable, reasons justifying deviations from the protocol-defined schedule (eg, temporarily increased glycemic target due to hypoglycemia unawareness) have to be documented in the patient's file.

Fasting SMPG will be measured by the patient/parent before breakfast or any administration of insulin.

Patients who experienced a non-severe hypoglycemia as a result of inadequate calculation of dose of mealtime insulin analogue against the carbohydrate content of a meal or due to a missed meal, unusual exercise or alcohol use will not have their insulin glargine (IMP) dose decreased and whenever appropriate will be counseled on the correction of those behaviors.

It may be prudent to temporarily increase glycemic targets for a patient if, for example, hypoglycemia unawareness or frequent episodes of hypoglycemia occur. In such situation new targets and the rationale behind should be documented in the patient file.

Sound clinical judgment is to be exercised while titrating doses of the IMP. Investigators may adjust or stop titration, or temporarily reduce dose if they believe further titration would be hazardous at that time; however, the rationale of deviating from the adjustment schedule should be documented in the patient file.

Patients and/or parents will be familiarized with the titration schedule so that they will be able to monitor and comply with the titration with the assistance of the investigator or medically qualified designee. During contacts (phone or on-site visits) with the study site, all dose adjustments should be discussed between the patient (and/or parent) and appropriate site personnel and be documented in the source document.

8.1.6 Switch-back to commercial basal insulin

Upon discontinuation of the study treatment, either scheduled or premature, patients must resume treatment with commercially available basal insulin. It is suggested that patients receiving Lantus will transition to commercial 100 U/mL formulation of basal insulin at 1:1 (Unit for Unit) rate (total daily basal insulin dose). Since with HOE901-U300 a slightly higher dose is needed to achieve comparable levels of glycemia, the total daily dose of replacement 100 U/mL insulin formulation should be reduced by 20% versus the last HOE901-U300 dose in order to reduce the risk of hypoglycemia in the initial period post transition. Further adjustments should be guided by SMPG and close glucose monitoring should be ensured during the initial weeks after the transition.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT

Mandatory additional insulin therapy is a fast-acting mealtime insulin analogue (glulisine, aspart or lispro) which is considered a Non-Investigational Medicinal Product (NIMP). Regular human insulin must not be used during the study.

8.2.1 Dosage schedule

Patients in both treatment groups will continue with their fast-acting mealtime insulin analogue during the study. The cost of the mealtime insulin analogue may be reimbursed if not covered by health insurance and if allowed by local regulations.

The area of injection for the fast-acting mealtime insulin analogue should be different from that of IMP (insulin glargine) so that any injection site reaction can be attributed specifically either to the fast-acting mealtime insulin or to IMP. As with IMP, site of mealtime insulin injections will be rotated within the injection area and areas will be changed periodically. Injection site reactions associated with administration of the IMP or NIMP, if any, will be reported as Adverse Events (see Section 10.4.1 and Section 10.6.3) and information on localization and insulin (IMP or NIMP) is required.

8.2.2 Starting dose

At baseline, when changing over from the pre-study basal insulin to the study basal insulin, doses of the fast-acting mealtime insulin analogue may remain the same.

8.2.3 Dose adjustment

Titration of mealtime insulin will occur at the investigator's discretion informed by instructions in the national product label and under consideration of the following general guidance, while avoiding hypoglycemia:

- While basal insulin doses are increased, fast-acting insulin doses may be reduced to avoid hypoglycemia particularly during daytime. The need for corrective doses may also be reduced.
- The dose of the mealtime insulin analogue (glulisine, lispro or aspart) is to be titrated based on SMPG data, including 2-hour postprandial plasma glucose results and the size or carbohydrate content of the meal. A scheme consistent with local guidelines and practices may be applied, eg, carbohydrate counting and a correction/supplemental scale for glucose out of goal range based on pre-meal SMPG. The scheme will be documented in the patient's file.
- The titration goal is a 2-hour postprandial SMPG of <180 mg/dL (10.0 mmol/L) while avoiding hypoglycemia. For the purpose of this protocol, 2 hours postprandial is defined as 2 hours after the start of the meal. If clinically indicated and if in line with local treatment guidelines, other individual goal for postprandial SMPG may be determined for a given patient; such individual goal needs to be documented in the patient's file.

The injection of the fast-acting mealtime insulin analogue in relation to meals will be done according to the individual habits of the patient, preferably prior to meal or snack. Occasional postprandial injection soon after meal intake may be done if deemed necessary and if allowed by the national product label.

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

After the end of the study treatment, doses of mealtime insulin may remain similar, however, if the study drug is replaced by NPH insulin, the potential for additive effects (eg, between morning NPH and lunchtime mealtime insulin) due to the peaked kinetics of the NPH, need to be taken into account.

8.3 TITRATION OVERVIEW AND EVALUATION OF PATIENTS NOT MEETING GLYCEMIC GOALS

The progress of titration will be regularly assessed by the sponsor personnel supported by a dedicated web-based tool, taking into account SMPG, insulin doses and hypoglycemia events which have been documented in the diary by the patients. Observed deviations from the titration schedule or unexpected trends will be communicated to the investigator. In addition, a central laboratory alert is set up to inform about inadequate glycemic control in terms of HbA1c exceeding the predefined level. The threshold value of HbA1c is defined as 8.5% from Visit 11 (Week 12) onwards.

In case of HbA1c above the target values and/or SMPG are not improving as expected in spite of successive IMP dose titration, the investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Pre-breakfast SMPG was actually measured in fasting condition (ie, after at least 8 hours fasting)
- SMPG are correctly categorized in the diary
- Compliance to treatment is appropriate:
  - IMP dose is adjusted according to the dosing schedule
  - NIMP dose is properly adjusted, including correction doses for pre-prandial glucose values above goal
- There is no inter-current disease which may jeopardize glycemic control (eg, infectious disease)
- Compliance to diet and lifestyle is appropriate, in particular, dosage adjustment for changes in carbohydrate content of the meal and SMPG

- If any of the above can reasonably explain the insufficient glycemic control, the investigator should undertake appropriate action, ie,:
    - Titrate the dose of IMP and/or NIMP
    - Set up adequate investigation and treatment of inter-current disease (to be reported in adverse event (AE)/serious adverse event (SAE)/concomitant medication parts of the e-CRF,
    - Stress the absolute need to be compliant to treatment, including the importance of consistency in meals and insulin dosing, particularly during this time of poor glycemic control, and compliance to lifestyle recommendations,
    - Consider additional monitoring of night time glucose,
    - Organize a specific interview with a specialist pediatric dietitian (or healthcare professional with documented experience in childhood diabetes) in particular with attention to awareness of the carbohydrate content of the meal and covering snacks with a dose of fast-acting mealtime insulin analogue,
    - Schedule HbA1c assessment at the next visit.

8.4 BLINDING PROCEDURES

Administration of all forms of insulin during the trial is to be open-label, and no attempt will be made to blind administration to investigators, patients and sponsor's and/or Clinical Research Organization local monitoring teams and auditors.

Despite the open-label administration of study insulin, assessment of outcomes, where possible, will be based on objectively collected data, which are assessments for HbA1c (primary endpoint) and FPG by a central laboratory blinded to study treatment groups.

The global sponsor study team will remain blinded with regards to the treatment arm of individual patients throughout the study (eg, patient's or cumulative tables or listings [such as AE or SAE listings] rendered accessible to facilitate data review will not bear study treatment identification). The members of the blinded endpoint assessment committee will review data in a blinded manner. Personnel involved in medical review of individual patients' data will have access to the treatment arm of patients whose events warranted CIOMS generation since CIOMS reports will include study treatment identification.

8.5 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Patients are randomized to receive during the 6-month treatment period and also during the 6-month extension period either HOE901-U300 or Lantus once daily in an open-label manner. The randomization ratio is 1:1. The randomization is stratified by HbA1c at screening (<8.5 versus ≥8.5%) and by age group at screening (<12 years versus ≥12 years).

Inclusion in the study is configured to ensure at least 30% of participants in the age range below 12 years. The randomized treatment kit number list is generated centrally by Sanofi. The IMPs are

packaged in accordance with this list. The Trial Supply Operations Manager provides the treatment kit number list, and the Study Biostatistician provides the randomization scheme (including stratification) to the Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS). Then, the IVRS/IWRS generates the patient randomization list according to which it allocates treatment groups to the patients.

The IMPs (HOE901-U300 or Lantus) are provided in open-label boxes and are identified with treatment kit numbers.

At the screening visit the investigator or designee has to contact the IVRS/IWRS center to receive the patient number. The patient identification (patient number) is composed of 12-digit number containing the 3-digit country code, the 4-digit center code and the 5-digit patient chronological number. If a patient who had previously failed screening is approached for re-screening, a new informed consent form must be signed by the parent (and assent obtained from the patient). In such case, a new patient number will be assigned by IWRS/IVRS.

On Visit 3 (Day 1), the IVRS/IWRS is contacted for randomization and for the first treatment kit(s) allocation. For each randomized patient, the IVRS/IWRS will allocate a treatment kit using their treatment kit number and a quantity of kit(s) to be dispensed corresponding to the same treatment group as assigned at randomization. After Visit 3 (Day 1) the IVRS/IWRS is contacted again each time a new treatment kit(s) allocation is necessary that is at Visit 11 (Week 12), at Visit 13 (Week 20), at Visit 14 (Week 26) and at Visit 16 (Week 38). IVRS/IWRS will be again contacted at Visit 18 (Week 52 or early discontinuation) for notification of the end of study treatment.

A randomized patient is defined as a patient who has been allocated to a randomized treatment by the IVRS/IWRS regardless whether the treatment kit was used or not. A patient cannot be randomized more than once in the study. A patient who needs to be moved to another site will have his/her randomization number assigned at the new site.

8.6 PACKAGING AND LABELING

The respective number of the study treatment will be packaged under the responsibility of Sanofi according to good manufacturing practice and local regulatory requirement. Lantus will be supplied in boxes of 2 disposable pens for insulin glargine 100 U/mL and HOE901-U300 will be supplied in boxes of 2 disposable pens for insulin glargine 300 U/mL.

The appropriate number of kits will be dispensed to cover up to the next dispensing visit. Storage conditions and use-by-end date are part of the label text.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements. Treatment labels will indicate the treatment number used for treatment allocation. The patient number, visit number and box number will be entered manually by the site staff on the treatment box label prior to dispensing.

8.7 STORAGE CONDITIONS AND SHELF LIFE

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

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor and are provided to study participants in the instruction for use leaflet together with the IMP injection pens.

The expiry date is mentioned on the IMPs labels, and storage conditions are written on the IMPs labels and in the instruction leaflet.

8.8 RESPONSIBILITIES

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

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

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

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

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

8.8.1 Treatment accountability and compliance

Returned and dispensed IMP will be documented into the Treatment Log Form. Investigator or delegate has to visually check the filling status of the cartridges in the pens in the returned packs and compare to dosing records documented in the patients' diaries. Discrepancies have to be addressed to the patient for clarification of real treatment administration. The investigator or designee completes the appropriate treatment log form based on the unused, used and in-use IMP (study drug pens) returned.

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

For the mandatory background fast-acting insulin analogue (NIMP) provided by the sponsor, a treatment log form will be completed and reconciliation will be performed.

For NIMP not provided by the sponsor, the following information will be captured in standard site documents and records: Study identification, patient identification (number or name/ initials), NIMP trade name, batch, start date, end date.

8.8.2 Return and/or destruction of treatments

Patients have to return all the used, in-use and unused IMP at each on-site visit including final assessment on-treatment visit (Visit 18 - either scheduled at Week 52 or in case of permanent premature discontinuation) (see Section 1.2).

All partially used and unused treatments will be retrieved by the Sponsor. A detailed treatment log of the returned IMP will be established with the investigator (or the pharmacist) and countersigned by the investigator and the Monitoring Team. The investigator will not destroy any IMP unless the Sponsor provides written authorization.

8.9 CONCOMITANT MEDICATION

A concomitant medication is any treatment, including vaccines, received by the patient concomitantly to the IMP.

Treatments in addition to the study treatment and NIMP should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the investigator, with a stable dose (when possible).

Any treatments, which are continued during the study and/or initiated or changed during the study, must be recorded in source data and in the e-CRF.

8.9.1 Concomitant Diabetes Therapy

See Section 8.2.

8.9.2 Prohibited concomitant therapy

The following drugs are not permitted during the study until the End of treatment visit (Visit 18 – Week 52 or early treatment discontinuation):

- Antihyperglycemic treatments other than the mandatory fast-acting mealtime insulin analogue (See Section 8.2), except the short-term use (ie, maximum 10 days) eg, during hospitalization, etc.
- Any basal insulin other than the IMPs, following randomization, except the short-term use (ie, maximum 10 days) eg, during hospitalization, etc.
- Insulin pump therapy
- Systemic glucocorticoid use for more than 10 days. Topical, inhaled or local (ie, formulations without major systemic effect lasting for more than 10 days) applications are allowed, regardless of duration of use.
- Weight loss drugs
- Any investigational study drug other than the IMP for this study

The need for use of prohibited therapy will result in the patient's withdrawal from the study treatment.

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

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

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

9.1 EFFICACY

The baseline value for efficacy variables will be the last available value obtained up to the date of randomization.

Observation periods for efficacy variables

- 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, 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 main 6-month randomized period for efficacy variables is defined from randomization date up to month 6 (Visit 14), regardless of study treatment discontinuation.
- 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.

9.1.1 Primary endpoint

HbA1c (change from baseline to endpoint [Month 6/Week 26]).

9.1.1.1 HbA1c measurement

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

HbA1c is assayed at screening (Visit 1, Week-2); at baseline (Visit 3; Day 1); at Visit 11 (Week 12); at Visit 14 (Week 26 primary endpoint assessment visit); at Visit 16 (Week 38) and at End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation).

9.1.2 Secondary endpoints

- Percentage of patients with HbA1c values of <7.5% at month 6 overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) symptomatic 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 month 6 (central laboratory);
- Percentage of patients with fasting plasma glucose (FPG) ≤130 mg/dL (7.2 mmol/L) at month 6 overall and without any episode of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L) symptomatic 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 month 6;
- Change in variability of 24-hour mean plasma glucose based on 8-point SMPG profiles from baseline to month 6;
- Change in 8-point self-monitored plasma glucose (SMPG) profiles per time-point from baseline to month 6 (pre-prandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, bedtime plasma glucose, nocturnal plasma glucose);

9.1.2.1 Fasting Plasma Glucose

Fasting plasma glucose is measured at a central laboratory.

Blood samples for FPG measurement are taken at baseline (Visit 3; Day 1), at Visit 14 (Week 26), and at End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation).

9.1.2.2 Self-measured plasma glucose (SMPG)

Glucose meter, patient diary and training

All the patients/parents are supplied with a glucose meter, the corresponding supplies (lancets, test strips, control solution, etc.) and with diaries at Visit 1 (Week -2) in order to perform self-measurement of plasma glucose, reporting hypoglycemic symptoms and record IMP/NIMP doses. It is recommended to perform tests with the control solution before first use of the study glucose meter, in cases when SMPG reading is considered incorrect or inconsistent with symptoms and whenever a new batch of test strips is used. If SMPG ≥252 mg/dL (14 mmol/L) is measured, measurement of blood ketones may be needed, please see detailed instructions in Section 10.6.2. During the study, all SMPG have to be done using the sponsor-provided glucose meter. The readings are to be transferred to the diary.

Patients/parents will be instructed on the proper use of the glucose meter and the diary including education around hypoglycemia symptoms (see Section 9.2.1) and management (see Section 10.6.1) at screening (Visit 1, Week-2); at baseline (Visit 3; Day 1) and the training

will be repeated as often as necessary at the study visits. The diary, blood glucose meter and blood ketone meter need to be brought to the study site at each on-site visit.

SMPG measurements include the following:

Fasting SMPG

The fasting (pre-breakfast) SMPG will be measured on at least 5 days in the week before each visit. It is recommended to perform fasting SMPG daily throughout the study. When up-titration has been completed and fasting (pre-breakfast) SMPG is stable in the target range, the number of fasting SMPG checks can be reduced according to the investigator's judgment, however at least 3 fasting (pre-breakfast) SMPG measurements per week should be performed.

During the screening period compliance to the fasting SMPG measurement schedule will be used to assess eligibility for entry in the randomized treatment period.

8-point SMPG Profiles

Eight-point blood glucose profiles should be measured at the following 8 time-points: between 01:00 and 04:00 AM at night; before and 2 hours after breakfast; before and 2 hours after lunch; before and 2 hours after dinner; at bedtime). Two hours post meal is defined as 2 hours after the start of the meal.

Patients are required to have 8-point SMPG profiles performed on at least one day in the week before the baseline visit, and the visits week 26 and week 52 (end of treatment). Special attention should be paid that the nighttime SMPG value (between 01:00 and 04:00 AM) is recorded.

On days when 8-point profiles are done, fasting SMPG will be considered as the second point of measurement, ie, "before breakfast" time point after the first point measurement at 01:00 – 04:00 AM at night.

SMPG during episodes of symptomatic hypoglycemia

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

Complementary SMPG

Patients are encouraged to continue with their usual pattern of SMPG measurements on top of protocol-mandated profiles. It is recommended to perform 4-6 SMPG daily at different times of the day and measure the nighttime SMPG once weekly for optimal control of glycemia and adjustment of the insulin regimen. Additional SMPG are recommended in association with exercise (before start of exercise, when need arises during exercise, after exercise and at bedtime) and, if deemed appropriate by the investigator, at sick days or menses (1, 7).

9.1.2.3 Dose of basal and mealtime insulin

Patients will record their basal insulin and mealtime insulin dosing data (time and dose), including corrective doses, in the diary daily during the screening period and during the treatment period up to Visit 11 (Week 12); at least over one week before each visit during the remainder of the treatment period until the End of Treatment visit (Visit 18 - Week 52 or early treatment discontinuation); over the first week of the post-treatment follow up period and on at least 2 consecutive days per week during the remainder of the follow up period.

9.2 SAFETY ENDPOINTS

The safety endpoints to be assessed are:

- Hypoglycemia (see Section 9.2.1),
- Hyperglycemia with ketosis (see Section 9.2.2)
- AEs (including injection site reactions and hypersensitivity reactions), SAEs and Adverse event of special interest (AESI) (see Section 10.4.1),
- Safety laboratory values (see Section 9.2.4),
- Anti-insulin Antibodies (AIA) (see Section 9.2.8),
- Physical examination (see Section 9.2.5),
- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP] and heart rate [HR]) (see Section 9.2.7),
- Body weight (see Section 9.2.6).

The baseline value for safety endpoints will be the last available value prior to the first dose of IMP.

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 open-label 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 open-label 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 open-label IMP (after the TEAE period).

9.2.1 Hypoglycemia

Hypoglycemia events will be categorized as follows using the criteria published by the ADA (4, 5) and ISPAD (1):

- **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) (8).

  Note that "cannot assist in their care" means that the severity of symptoms prevents self-treatment by a child/adolescent who is otherwise capable of managing his or her episodes of hypoglycemia. Assisting a patient out of kindness, when assistance is not required, should not be considered a "severe hypoglycemia" incident.

  Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

  Any hypoglycemic event which leads to unconsciousness, coma, or seizure must be reported as an SAE. In addition, any hypoglycemic event, which at investigator discretion, qualifies as serious adverse event must also be reported as an SAE.

- **Documented symptomatic hypoglycemia**

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

  Clinical symptoms that are considered to result from a hypoglycemic episode could be: cold sweatiness, pallor, pounding heart, tremor/trembling, headache, nausea, difficulty concentrating, blurred or altered vision, slurred speech, difficulty hearing, unsteady gait, altered judgment and confusion, irritability, erratic behavior, nightmares, inconsolable crying, seizures, unconsciousness, coma.

- **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.

  In addition the composite category of severe and/or documented (SMPG <54 mg/dL; 3.0 mmol/L and ≤70 mg/dL; 3.9 mmol/L) symptomatic hypoglycemia will be presented.

  All documented hypoglycemia categories will be also evaluated for the more stringent SMPG threshold of <54 mg/dL (3.0 mmol/L). Details of all hypoglycemia events will be reported on dedicated e-CRF pages.

  Instructions on hypoglycemia collecting and reporting are described in Section 10.6.1.

  All hypoglycemia events reported by investigator as severe and/or reported as serious adverse events will be independently reviewed by an external expert pediatrician specialized in diabetology blinded to treatment arm (see Section 9.2.9).

9.2.2 Hyperglycemia with ketosis

If SMPG is ≥252 mg/dL (≥14 mmol/L) in an unwell child (eg, feeling sick or nauseated) or when persistent blood glucose values ≥252 mg/dL (14 mmol/L) without substantial decline are present over a period of approximately 60-120 min after an extra dose of rapid-acting insulin analogue, or when a patient is ill with fever and/or vomiting, capillary blood ketones will be measured using a meter provided by the sponsor. Hyperglycemia with ketosis is defined as self-measured plasma glucose ≥252 mg/dL (14 mmol/L) with accompanying self-measured blood ketones ≥1.5 mmol/L.

Instructions on collecting and reporting events of hyperglycemia with ketosis are described in Section 10.6.2.

9.2.3 Adverse events

Adverse events, serious adverse events and adverse events of special interest will be collected from the time of informed consent signature and then at each visit until the end of the study.

Refer to Section 10.4, Section 10.5 and Section 10.6 for details.

9.2.4 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry) and urinalysis. Samples will be collected for central laboratory in accordance with the study schedule and values will be analyzed after conversion into standard international units.

The following laboratory safety variables will be analyzed:

- Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets at screening (Visit 1, Week -2); Visit 14 (Week 26) and End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation);
- Clinical chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), AST (Aspartate aminotransferase), ALT (Alanine aminotransferase), ALP (Alkaline phosphatase), creatinine, estimated glomerular filtration rate (eGFR) (Schwartz equation) (9), sodium, potassium, calcium, chloride at screening (Visit 1, Week -2); Visit 14 (Week 26) and End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation);
- C-peptide (Visit 3, Day 1);
- Urine (for analysis including pH, glucose, ketones, leucocytes, blood/hemoglobin, protein) will be collected at screening (Visit 1, Week -2) and End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation);
- Urine albumin/creatinine ratio assessment and microalbuminuria (to be done on first morning urine sample) will be performed at baseline (Visit 3, Day 1);
- Serum pregnancy test (at screening [Visit 1, Week -2]) and urine pregnancy test (at study site; each onsite visit thereafter) in post-menarchal girls;
- In addition, hepatitis B surface antigen (HBsAg) and Hepatitis C viral antibodies (HCAb) (and reflex test for Hepatitis C virus RNA in case of positive HCAb) laboratory data will also be collected only at screening visit (Visit 1, Week -2) for identifying patients with exclusion criteria or safety consideration.

Note: Any abnormal laboratory value estimated as clinically significant by the investigator should be immediately rechecked (whenever possible using the central laboratory) for confirmation before making a decision of permanent discontinuation of IMP for the concerned patient. Any confirmed laboratory abnormality estimated as clinically significant by the investigator must be reported as an AE/SAE as applicable. Please also refer to Section 10.4.1.

9.2.5 Physical examination and Tanner puberty stage

Physical examination is performed at screening (Visit 1, Week -2); at baseline (Visit 3, Day 1), at Visit 14 (Week 26) and at End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation). The date of menarche will be captured if applicable.

Tanner puberty stage is assessed at baseline (Visit 3, Day 1), Visit 14 (Week 26) and Visit 18 (Week 52 [and at early treatment discontinuation visit if the previous assessment did not occur within the previous 3 months]) (see Section 1.2). Once the adult stage is determined, defined by Tanner stage 5 (see Appendix A), no further assessments will be performed.

9.2.6 Body Weight and Height

The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer.

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The weight is read and recorded in the e-CRF and Source Data. Self-reported weights are not acceptable; patients/parents must not read the scales themselves.

Body weight is measured at screening (Visit 1, Week -2), baseline (Visit 3, Day 1), Visit 11 (Week 12), Visit 14 (Week 26), Visit 16 (Week 38) and End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation). Height is measured at screening (Visit 1, Week -2), at Visit 11 (Week 12), Visit 14 (Week 26), Visit 16 (Week 38) and End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation). Body mass index (BMI) will be determined based on body weight and height.

9.2.7 Vital signs

Vital signs include: systolic and diastolic blood pressure (mmHg) and heart rate (beats per minute: bpm). They are assessed at screening (Visit 1, Week- 2) and at each on-site visit thereafter (see Section 1.2). Blood pressure (mmHg) should be measured on right arm when the patient has been sitting quietly for 5 minutes, and is seated with his or her back supported, feet on the floor and right arm supported, cubital fossa at heart level. Measurement should be taken under standardized conditions, approximately at the same time of the day, with the same device (regularly recalibrated according to manufacturers´ instructions) using the cuff appropriate to the size of the patient’s upper right arm and the values are to be recorded in the e-CRF. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) should be recorded. The preferred method of blood pressure measurement is auscultation.

Heart rate (bpm) will be measured at the time of the measurement of blood pressure and also is to be reported in the e-CRF.

9.2.8 Immunogenicity

Anti-insulin antibodies (AIA) will be determined at a centralized laboratory using a validated anti-insulin antibody immunogenicity assay.

Blood samples for immunogenicity tests will be collected prior the first administration of HOE901-U300 or Lantus (during the baseline visit [Visit 3]) and at Visit 11 (Week 12), Visit 14 (Week 26) and End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation). The samples should be taken prior to administration of the basal insulin (applicable to patients who have their basal insulin injection in the morning) and at least four hours after last dosing of the fast-acting mealtime insulin analogue (insulin glulisin, insulin lispro, insulin aspart).

Detailed procedure of sample preparation, storage and shipment will be described in the specific laboratory manual. Two (2.0) ml blood volume is to be collected for each anti-insulin antibody sample.

The AIA endpoints will be detailed in the Statistical Analysis Plan.

9.2.9 Blinded external endpoint assessment committee

Ongoing safety surveillance will be performed by a blinded external endpoint assessment committee consisting of experts in pediatric diabetology and endocrinology:

- The ISPAD definition of severe hypoglycemia is broad and includes a subjective element: 'The child has altered mental status and cannot assist in his own care', and determining whether an episode fulfils the definition can be challenging, especially in young children. Therefore, all reported episodes of severe hypoglycemia will be reviewed in a blinded manner by the external safety monitoring group, in order to determine whether the episodes fulfilled the criteria for severe hypoglycemia. For this purpose the experts will be provided on a regular basis with a tabulated overview of hypoglycemia events.

To monitor general safety of the study participants, the committee will be provided on a regular basis with tabulated overviews of TEAEs, serious TEAEs.

The committee will also assess the antigenicity data (AIA data and potential clinical correlates [hypersensitivity events, indicators of insulin-resistance]).

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics sparse sampling

The concentration of Insulin glargine and its metabolites (M1 and M2) in plasma will be measured using a validated LC-MS (Liquid Chromatograph Ion Spray Mass Spectroscopy) assay with an LLOQ (Lower Limit of Quantitation) of 0.2 ng/mL. One (1) mL of blood should be collected at each PK sampling time according to the below schedule.

PK sparse sampling will be proposed to all randomized patients and will be collected over a single day in those participants who consent to this assessment after the end of titration phase during the period when only minor adjustments of the basal insulin dose are done to maintain the glycemic control (ie, no sooner than at Visit 13, Week 20, but no later than at Visit 14, Week 26,). All participants who provided an assent and whose parents signed the specific informed consent form (see Section 12.2), will provide 3 blood samples. Patients will be offered to stay at the study site throughout the day when the procedure is performed and meals will be provided to patients. The day of the PK sparse sampling procedure within the authorized window will be agreed between patient/parent and investigator. The sample times will depend on the existing basal insulin dosing regimen:

- Patients with IMP dose administered in the evening (~8:00 PM) on the day before the date of the visit: patients can have breakfast (including mealtime insulin injection) at home and come to the study site in the morning to have blood samplings at around 8:00AM, 12:00 PM, 04:00 PM (what corresponds with samplings 12 h, 16 h and 20 h after the last basal insulin injection). Sample times can be within ±1 h.
- Patients with IMP dose administered in the morning (~8:00 AM) on the day of the visit: patients will come to the study site in the morning in fasting condition not having injected their basal and mealtime insulin to have blood samplings at around 8:00AM, 12:00 PM, 04:00 PM (what corresponds with pre-dose sampling [to be done within 1 h before time of dosing] and 4 h and 8 h post dose sampling). Sample times can be within ±1 h.

9.4 APPROPRIATENESS OF MEASUREMENTS

The primary efficacy endpoint of this study is change of HbA1c from baseline to endpoint (Week 26/Month 6). HbA1c reflects the average glycemia over 2-3 months and has strong predictive value for diabetes complications. It is accepted by regulatory agencies as an appropriate primary endpoint to support a claim based on glycemic control. Twenty six weeks duration of study treatment is considered to be sufficient for achieving steady state conditions with HOE901-U300 or Lantus enabling an adequate assessment of time-dependent changes in HbA1c and the concomitant risk of hypoglycemia.

Analysis of responders (HbA1c) is set up to compare both formulations in terms of rate of patients achieving and/or maintaining optimal long-term glucose control confirmed by target HbA1c <7.5% at month 6 overall as well as not compromised by severe and or documented (SMPG <54 mg/dL; 3.0 mmol/L) symptomatic hypoglycemia during the last 3 months of the main 6-month treatment period.

Fasting plasma glucose (FPG): change from baseline to Month 6/Week 26 and rate (%) of patients reaching target FPG at month 6 without hypoglycemia. Change in FPG is an acceptable secondary efficacy endpoint by regulatory agencies.

Studies have demonstrated that frequent SMPG measurements correlate with decreased HbA1c. Thus it is recommended that regardless of mandatory SMPG measurements patients regularly perform 4-6 SMPG at different times of the day (7).

Incidence of patients with nocturnal hypoglycemia: one of the limiting factors in achieving desired glycemic control in patients treated with insulins, including basal insulins, is a risk of hypoglycemia, especially nocturnal hypoglycemia. Even distribution of the glucose lowering activity over the 24 hour injection intervals following once daily administration of HOE901-U300, as demonstrated in phase 1 studies, is expected to reduce the rate of hypoglycemia, including nocturnal hypoglycemia. Lower risk of nocturnal hypoglycemia may result in better adherence to antidiabetic therapy and increase chances of reaching glycemia targets resulting in reduced risk / delayed onset of chronic complications of diabetes. Two nocturnal hypoglycemia categories will be taken into account for analysis: defined by the time of the day (between 00:00 and 05:59 a.m.) and defined by sleep status (waking up the patient after going to bed in the evening and before getting up in the morning).

Safety will be evaluated by standard clinical and laboratory measurements including assessment of parameters of interest for a glucose lowering injectable peptide such as injection site reactions and hypersensitivity reactions. A special attention will be paid to the most prominent limiting factor in achieving optimal glycemic control, ie, hypoglycemia. Hypoglycemia (incidence and rate) will be assessed according to categories defined by the ADA (4) and (5). Documented hypoglycemia categories will be assessed using two plasma glucose thresholds: <54 mg/dL (3.0 mmol/L) and ≤70 mg/dL (3.9 mmol/L).

In established T1DM the estimated incidence of DKA is 1-10% per patient per year (10); DKA is a special safety concern in the pediatric population. Incidences of hyperglycemia with ketosis (defined as self-measured plasma glucose ≥252 mg/dL [14 mmol/L] with accompanying self-measured blood ketones ≥1.5 mmol/L), which may indicate the risk of developing DKA, will be assessed.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The visit schedule and comprehensive list of procedures/assessments is presented in the "Study Flow Chart" in Section 1.2.

This is an outpatient study and consists of 7 on-site visits and 13 phone-call visits. Phone-call visits can alternatively be performed as on-site visits. Additional contacts (phone, on-site visit) will be made available for patients' in-between the scheduled visits as needed. Patients should be accompanied by parent/legal guardian[2] during each scheduled visit/contact. In case a patient does not show up for a visit or cannot be reached for a phone visit, the investigator has to make three phone call attempts and send a certified letter in order to locate the patient.

All on site visits should take place in the morning at approximately the same time. The patient has to be in fasting condition for the following on-site visits: Visit 3 (baseline), Visit 11 (Week 12), Visit 14 (Week 26) and End of treatment Visit 18 (Week 52 and, if applicable, early treatment discontinuation); timing of fasting on-site visits should be agreed with patients/parents to reduce risk of hypoglycemia and to prevent non-compliance with fasting requirements due to extension of fasting period if such visit is scheduled relatively late as compared to the patient's daily routine. The fasting condition is defined as an overnight fast of at least 8 hours that consisted of no food or liquid intake, other than water. IMP and NIMP should be administered after the fasting blood sample is drawn for all laboratory tests at the study site at visits where such sampling is scheduled.

Note: If the patient is not fasting at Visit 3 (baseline), a new appointment should be given to the patient for the following day if possible, with instruction to be fasted. If the patient is not fasting at the remaining visits specified above, the planned study procedures/assessments except collection of blood for central laboratory may be performed and a new appointment should be given to the patient for the following day if possible, with instruction to be fasted.

Nutritional and lifestyle advice will be provided by a specialist pediatric dietitian (or healthcare professional with documented experience in childhood diabetes) as needed by the patients/parents and when deemed appropriate according to the investigator's judgment.

Visit window: Visit 3 (baseline) will take place 14 ± 3 days after Visit 1 (screening); from Visit 4 (Week 1) to Visit 11 (Week 12; inclusive), a timeframe of ± 3 days is acceptable and from Visit 12 (Week 16) up to Visit 18 (Week 52), a time frame of ± 5 days is acceptable using the day of Visit 3 (Day 1, baseline) as reference (if one visit date is changed, the next visit should take place according to the original schedule). During the post-treatment follow-up period, for Visit 19 (Follow-up 1 visit) a time frame of +2 day is acceptable and for Visit 20 (Follow-up 2 visit) a time

[2] "Legal guardian" means an individual or judicial or other body authorised under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research. In this document "parent" will be used as a synonym for "legal guardian"

frame of ± 5 days is acceptable using the day of Visit 18 (scheduled at Week 52 or early treatment discontinuation, as applicable) as reference.

Starting from the time when the informed consent has been obtained, AEs/SAEs will be recorded at each visit. Hypoglycemia will also be recorded all along the study. Appropriate e-CRF pages (visit-specific pages and whenever applicable also non visit-specific pages such as adverse event, hypoglycemia, medication pages) need to be completed during the patient's visit or shortly thereafter, except SAE or AESI which have to be reported within 24 hours. E-CRF reporting instructions and timelines are described in a separate document.

10.1.1 Screening period

Patients meeting all the inclusion criteria are candidates for the screening phase. All laboratory tests measured at a central laboratory that are needed for checking the exclusion criteria of the patients are performed at the screening Visit 1 (Week -2).

As an exception, if any of the laboratory parameters required for assessment of eligibility are not available by the date of scheduled baseline (V3) visit (eg, lost specimen, non-assessable sample, etc.), a retest can be performed and the screening period can be extended by one additional week.

Patients can be re-screened one time before randomization in case of non-evaluable exclusion criteria or in cases where original screen failure was due to reasons expected to change at rescreening and based upon the investigator's clinical judgment. Re-screened patients will be subject to the screening visit procedures/assessments (see below) including new informed consent form signed and new assent obtained and allocation of a new patient number. In case of adolescents who will reach the legal age of maturity during the study and are subject to transition from pediatric to adult health care, before the patient can be screened, the investigator has to ensure that the patient may continue to attend planned study visits and undergo study procedures at the study site according to the protocol until the planned last study visit.

10.1.1.1 Screening visit (Visit 1, Week - 2)

The patient should come to the study site in the morning.

The following procedures/assessments will be performed and recorded at this visit:

- Informed consent/assent:
  - The patient and the parent(s) will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration. Message to patients will be adapted to their individual level of comprehension. Written information will be provided to the parent(s) and, if applicable, written assent will be provided to the patient. Written informed consent form must be signed by the parent and investigator prior to any investigations. Written assent (when applicable) also must be signed by the patient and investigator prior to any investigations. Younger children for whom the written assent does not apply may only be screened if oral assent has been obtained in presence of an impartial witness (see Section 12.2).

- Assessment of Inclusion/Exclusion criteria; whenever available, laboratory reports confirming presence of antibodies indicative of T1DM will be documented in source documents;
- IVRS/IWRS contact:
  - IVRS/IWRS will be contacted for notification of screening and patient number allocation (see Section 8.5). Please note that it is important to have the IVRS/IWRS contact before any blood sample is drawn because the patient number is given by IVRS/IWRS and it must be reported on the laboratory requisition forms.
- Demography, diabetes and medical/surgical history, allergy history, alcohol and smoking habits:
  - Demography data such as birth date, gender and race will be collected.
  - Collection of diabetes history will include documentation of duration of diabetes, antibody status and C-peptide at diagnosis (provide a copy of results if available), basal and mealtime insulin regimen, and history of acute and microvascular complications.
  - Medical/surgical history including patient's allergy history and patient's family allergy history will be recorded. Data for alcohol habits during the last 6 months before screening visit and smoking habit will be collected.
- Previous (within the previous 3 months) and concomitant medication history (other than insulin), including doses and regimen,
- Physical examination; the date of menarche, if applicable, will be captured,
- Body weight and height; see Section 9.2.6,
- Vital signs (SBP and DBP, HR); see Section 9.2.7,
- Central laboratory testing: blood and urine sample is collected for all scheduled central laboratory tests, including:
  - HbA1c,
  - Safety laboratory test for hematology, serum chemistry and urinalysis,
  - HbsAg and HCAb tests (including confirmatory sample for Hepatitis C RNA in case of positive result of the HCAb screening sample),
  - Serum pregnancy test in post-menarchal girls,
- Information on acceptable measures preventing pregnancy (see Appendix B) to postmenarchal girls and their parents and documentation;
- Dispensation of blood glucose meter (including related material) and instruction on the proper use, including recommendations concerning tests with the control solution (see Section 9.1.2.2),
- Explanation of symptoms suggestive of hypoglycemia, and instruction on the management of episodes of hypoglycemia (see Section 10.6.1),

- Dispensation of a blood ketone meter (including related material) and instruction on the proper use (see Section 10.6.2), education around prevention of hyperglycemia,
- Nutritional and lifestyle advice (as needed),
- Dispensation of a patient diary. Study patients will be given detailed instruction on use of the diary including what information need to be reported. The diary includes sections for time and dose of basal and mealtime insulin injections, time, value and attribution of scheduled and unscheduled SMPG, time and value of self-measured blood ketones, details of hypoglycemia.
- Instruction on SMPG schedule (see Section 9.1.2.2),
- Dispensation of urine container and instruct them how to collect at home in the morning of patients' first morning urine and to bring the urine sample to the site at randomization visit (Visit 3).

An appointment is given to the patient/parent for the next two visits: phone-call visit 2 (Week -1) and baseline visit (Day 1). The patient is to come to the study site for the baseline visit (Visit 3, Day 1) 14 days ± 3 days after the date of Visit 1 in fasting condition. The patient/parent is instructed to bring container with patient's first morning urine, the glucose meter, the ketone meter, the diary and patient's current anti-diabetic medications.

10.1.1.2 Telephone visit 2 (week -1)

Approximately one week after the screening visit the patient/parent is called by the investigator or qualified designee at a scheduled time. If the call has been completed by site staff other than the investigator, the investigator has to be consulted if AE/SAE is suspected. This visit is a mandatory telephone visit, but can optionally be performed as a clinical visit.

During the phone call the following points have to be addressed with the patient/parent:

- Did you/your child experience any new medical event, disease or symptom since the last visit? (Please pay attention to any possible hypoglycemic event or symptom).
- Did you/your child experience any change in a preexisting medical event or disease or symptom since the last visit?
- Did you/your child change or add any concomitant medication since the last visit? What are the actual basal and fast-acting mealtime insulin analogue doses?
- Do you/your child feel comfortable in handling the diary, glucose meter and ketone meter or do you need any more explanation?
- The patient/parent is asked about fasting SMPG values and, if available, other SMPG values from the last week (if SMPG ≥252 mg/dL [14 mmol/L] was measured when the child was unwell or when persistent blood glucose values ≥252 mg/dL (14 mmol/L) without substantial decline were present over a period of approximately 60-120 min after injection of an extra dose of rapid-acting insulin analogue, or when the patient was ill with fever and/or vomiting, check if blood ketones were measured, too).

Further following procedures will be performed:

- Review of Inclusion/Exclusion criteria.
- If based on the glycemic data, adjustment of insulin doses is needed, the investigator instructs patients/parents on the new insulin doses.
- The patients/parents are reminded to measure required SMPG and if applicable blood ketones and complete the diary.
- Diary data available in the e-CRF are reviewed (basal insulin dose, NIMP dose, SMPG values (see Section 9.1.2.2), hypoglycemia events, blood ketone values (see Section 10.6.2).
- Change of concomitant medications is documented in the e-CRF.
- AE/SAE if any are reported.

Furthermore, an appointment for the baseline visit (V3, Day 1) in fasting condition at study site in one week is confirmed with the patient/parent. The patient/parent is reminded to bring container with patient's first morning urine, the glucose meter, the ketone meter, the diary and patient's current anti-diabetic medications. The patient/parent will be reminded not to inject any insulin in the morning of the visit.

If a patient is found ineligible and thus considered a screen failure, the patient must not enter the randomized treatment phase and IVRS/IWRS has to be contacted as soon as possible in order to register the patient as a screening failure.

10.1.2 Open-label randomized treatment phase (Day 1 to Week 52)

The open-label randomized treatment phase consists of two periods: the main 6-month treatment period spanning from baseline (Visit 3 [Day 1]) to the primary endpoint assessment (Visit 14 [Week 26]) and the on-treatment safety extension period starting after the primary endpoint visit and lasting until the end of treatment visit (Visit 18, Week 52).

Patients meeting all inclusion criteria and with no exclusion criteria at the end of the screening period are eligible to be enrolled into the open-label randomized treatment phase.

At Visit 3 (Day 1), patients/parents must demonstrate competence in the unaided use of the injection device, including dose setting and the proper use of glucose meter, ketone meter and the diary before randomization may occur.

Training will be repeated as often as deemed necessary by study site staff during the treatment period.

10.1.2.1 Baseline visit (Visit 3, Day 1)

At this visit, the patient must return to the investigation site in the morning in fasting condition. Patients who inject their pre-study basal insulin in the morning (either as once daily or more than once daily regimen) will come to the study site without having injected the morning dose of basal insulin.

Patients accompanied by parent will come with the blood glucose meter, ketone meter, the diary, current anti-diabetic medications and with the first-morning urine sample of the same day.

The following procedures/assessments will be performed and recorded at this visit:

- Review of all inclusion/exclusion criteria
- Determination of the starting dose of the IMP
- IVRS/IWRS contact

Call IVRS/IWRS for randomization, investigational medicinal product starting dose has to be established before contacting IVRS/IWRS (see Section 8.1.4).

The IMP (either HOE901-U300 or Lantus) will be given at an individually titrated dose by SC injection once daily either in the morning or in the evening at the same time every day. It is expected that patients taking their pre-study basal insulin once daily in the morning will continue with the morning regimen of the IMP during the study as well as patients taking their pre-study basal insulin once daily in the evening will continue with the evening regimen. At Visit 3 (baseline) patients receiving more than one daily injection of their pre-study basal insulin will change to once daily injection either in the morning or in the evening, at the discretion of the patient/parent/investigator. Patients will stick with either morning or evening injections throughout the whole study treatment duration. The dosing interval between once daily injections of the IMP should be kept close to 24 hours as much as possible. Patients will continue with their mealtime fast-acting insulin analogue which is not to be changed during the study.

Patients switching from more than once daily basal insulin regimen, who wish to adopt a once daily evening administration schedule, will not use any basal insulin in the morning of the baseline visit and start HOE901-U300 or Lantus injection in the evening of the baseline visit. For those patients who wish to adopt a once daily morning administration schedule, the first administration of the IMP will take place at the end of the baseline visit, after scheduled laboratory samples have been drawn, at a reduced dose (approximately -20% of the calculated starting dose [see Section 8.1.4] or at the discretion of the investigator) taking into account changeover from more than once daily to the once daily regimen with the previous injection in the evening the day before.

- Blood sampling for:
  - HbA1c
  - FPG
  - C-peptide
  - Anti-insulin antibody

- Collect urine sample for albumin/creatinine ratio
- Urine pregnancy test (postmenarchal girls)
- Review of measures preventing pregnancy (see Appendix B) (postmenarchal girls)
- Physical examination including determination of Tanner puberty stage (see Section 9.2.5)
- Body weight
- Vital signs (SBP and DBP [in sitting position], HR)
- Review of diary data reported by the patient in the diary (basal insulin dose, NIMP dose, SMPG values (see Section 9.1.2.2), hypoglycemia events, blood ketone values (see Section 10.6.2)
- Collect and report in the e-CRF AE/SAE if any
- Record in the e-CRF names of basal and mealtime insulins
- Document in the e-CRF new or change in concomitant medication, if any
- Patient/parent training and education on self-injection devices, diary, blood glucose meter and blood ketones meter
- Diet and lifestyle counseling (as needed)
- Dispense boxes with prefilled disposable pens with the study drug
- Dispense glucose meter-related and ketone meter-related material (lancets, control solution, test strips, etc.) as needed
- Explanation of study treatment administration
  - Fixing of time point of once daily administration (see Section 8.1.3)
  - Explanation of dose titration (see Section 8.1.5)

Instruction to document details of problems experienced with the IMP injection device (see Section 8.1.2.1)

Telephone visit within 1 week ± 3 days after baseline (Visit 4) is to be appointed with the patient/parent and the schedule of subsequent telephone visits is reviewed. Remind the patient to perform scheduled SMPG (see Section 9.1.2.2) and blood ketones measurements whenever applicable (see Section 10.6.2).

Instruct the patient to bring the glucose meter, the ketone meter, the diary, the used and in use IMP and their current fast-acting mealtime insulin analogue for each visit to the study site (scheduled or unscheduled).

10.1.2.2 Phone call visits: Visit 4-10 (Week 1-10), Visit 12 (Week 16), Visit 15 (Week 32) and Visit 17 (Week 45)

The patient/parent is called by the investigator or qualified designee at a scheduled time. If the call has been completed by site staff other than the investigator, the investigator has to be consulted if AE/SAE is suspected and informed in case AE/SAE occurred. A phone call visit can be performed as a clinical visit if such need is expressed by the patient/parent (eg, need for nutritional and lifestyle advice) or for other reasons as deemed appropriate by the investigator.

During the phone call, answers to the following questions are to be obtained from the patient/parent:

- Did you experience any new medical event, disease or symptom since the last visit (please pay attention to any potential hypoglycemic events, potential allergic or injection site reaction)?
- Did you experience SMPG ≥252 mg/dL [14 mmol/L] while you were unwell (eg, you felt sick or nauseated; you had abdominal pain) or did you have persistent blood glucose values ≥252 mg/dL (14 mmol/L) without substantial decline over a period of approximately 60-120 min after injection of an extra dose of your rapid-acting insulin analogue or were you ill with fever and/or vomiting? If yes, did you measure and record the level of blood ketones?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you experience any problems using the IMP injection device?
- Did you adjust IMP since last visit? What are your actual IMP and mealtime insulin doses?
- Did you change or start any concomitant medication since the last visit?
- Do you feel comfortable in handling the diary, glucose meter and ketone meter or do you need any more explanation?
- Data entered by the patient in the diary are reviewed.

The phone visits will also include:

- Diary data available in the e-CRF are reviewed (IMP and NIMP dose, SMPG values (see Section 9.1.2.2), hypoglycemia events, blood ketone values (see Section 10.6.2).
- IMP treatment kit number(s) are documented in the e-CRF.
- Change in concomitant medications, if any, is documented in the e-CRF.
- Documentation and reporting of AE/SAE, PTC associated with the IMP pen if any.

The patient/parent will be instructed to:

- Perform required SMPG measurements (see Section 9.1.2.2), and ketones measurement whenever SMPG is ≥252 mg/dL (14 mmol/L) while feeling unwell (eg, sick, nauseated, abdominal pain) or when persistent blood glucose values ≥252 mg/dL (14 mmol/L) without substantial decline are present over a period of approximately 60-120 min after injection of an extra dose of rapid-acting insulin analogue or when being ill with fever and/or vomiting,
- Complete daily the diary
- Inject (self-injection by the patient or injection by the parent) once daily IMP at the dose prescribed by the investigator,
- Contact the site in case of occurrence of adverse event or problem with the IMP injection device and return to the site as deemed appropriate.

Give an appointment to the patient/parent for subsequent visits (on-site visit or phone call visit) and remind them to come for on-site visits in fasting condition (except on-site Visit 13 [Week 20] and Visit 16 [Week 38], when fasting is not required) not having injected the basal insulin for at least 8 hours and holding mealtime insulin, and to bring the glucose meter, ketone meter, the diary, the used, in use and unused IMP and their current fast-acting mealtime insulin analogue.

10.1.2.3 On-site Visits: Visit 11 (Week 12); Visit 13 (Week 20); Visit 14 (Week 26 – main study endpoint visit); Visit 16 (Week 38)

The patient (accompanied by the parent) must return to the investigation site in the morning of each on-site visit after randomization in fasting condition (except on-site Visit 13 [Week 20] and Visit 16 [Week 38] when fasting is not needed).

The following procedures/assessments will be performed and recorded at each on-site visit:

- Counting and collecting used and unused study drug disposable pens
- Review of data entered in the diary with the patient/parent (IMP and NIMP dose, SMPG values [see Section 9.1.2.2], hypoglycemia events, blood ketone values [see Section 10.6.2])
- Compliance check (IMP and NIMP dosing; SMPG; ketones measurements) and re-training as needed
- IMP treatment kit number(s) are documented in the e-CRF
- Ask for new or change in concomitant medications and document change in the e-CRF, if any
- Collect and report in the e-CRF AE/SAE, if any, including injection site reactions and possible allergic reactions as well as PTC associated with the IMP pen if any
- Nutritional and lifestyle advice by a specialist pediatric dietitian (or healthcare professional with documented experience in childhood diabetes): anytime when needed by the patient/parent and when deemed appropriate by the investigator

- IVRS/IWRS contact for allocation of treatment kit and dispensation of treatment kit
- Dispensation of glucose meter-related and ketone meter-related material (lancets, control solution, test strips, etc.) as needed
- Body weight and height (except Visit 13 [Week 20])
- Vital signs (SBP and DBP [in sitting position], HR)
- Physical examination (Visit 14 [Week 26] only)
- Determination of Tanner puberty stage (Visit 14 [Week 26] only), (see Section 9.2.5)
- Review of measures preventing pregnancy (see Appendix B) in postmenarchal girls
- Blood sample for Central Laboratory assessments (except Visit 13 [Week 20]) (see Section 9.2.4)

  Note: particular attention needs to be paid to ensure availability of the primary and secondary efficacy laboratory parameters (ie, HbA1c and FPG) scheduled for the main study endpoint visit (Visit 14 [Week 26]). If for instance the patient is not fasting, the blood sample will not be collected and a new appointment has to be given to the patient for the following day if possible, with instruction to be fasted. If the sample is not analyzable or the result is not available (eg, sample lost during shipment), an appointment needs to be given in order to perform a retest sample as soon as possible.

- Urine pregnancy test (post-menarchal girls)
- PK sparse sampling (optional). PK sparse sampling will take place after the end of titration phase, on the day of the on-site Visit 13, Week 20 or on the day of Visit 14, Week 26 or additional admission may be appointed according to patient/parent and investigator's preference during the period between these visits. See Section 9.3.1.

Education on self-injection, the use of glucose meter, ketone meter, diary will be repeated when necessary throughout the study.

During the on-treatment safety extension period when on-site visits are planned every 3 months, instruct the patients/parents to contact their investigators in case of occurrence of any AE and symptomatic hypoglycemia, missing the IMP dose, changing the dose or adding/changing any concomitant medication.

The patient/parent is reminded to perform scheduled SMPG measurements (see Section 9.1.2.2) and blood ketones measurements whenever applicable (see Section 10.6.2) and to complete the diary daily.

Upon completion of each on-site visit, an appointment for the next visit (on-site visit or phone call visit) will be made. Patients are instructed to come at next on-site visit in fasting condition (except Visit 13 [Week 20] and Visit 16 [Week 38] when fasting is not needed) not having injected basal insulin within 8 hours prior to the visit and holding mealtime insulin until after blood is drawn for all laboratory tests, and to bring the glucose meter, ketone meter, the diary, the used and unused IMP and their current fast-acting mealtime insulin analogue.

10.1.2.4 End of Treatment Visit (Visit 18, Week 52) or Early Treatment Discontinuation Visit

The following procedures/assessments will be performed and recorded at this visit:

- Counting and collecting used and unused study drug disposable pens
- Review of data entered in the diary with the patient/parent (IMP and NIMP dose, SMPG values [see Section 9.1.2.2], hypoglycemia events, blood ketone values [see Section 10.6.2])
- Document in the e-CRF IMP treatment kit number(s)
- Ask for new or change in concomitant medications and document change in the e-CRF, if any
- Collect and report in the e-CRF AE/SAE, if any, including injection site reactions and possible allergic reactions as well as PTC associated with the IMP pen if any.
- Nutritional and lifestyle advice by a specialist pediatric dietitian (or healthcare professional with documented experience in childhood diabetes): if needed by the patient/parent and if deemed appropriate by the investigator
- IVRS/IWRS contact for notification of end of open-label treatment period
- Body weight and height
- Vital signs (SBP and DBP [in sitting position], HR)
- Physical examination
- Determination of Tanner puberty stage (see Section 9.2.5)
- Blood and urine sample for Central Laboratory assessments (see Section 9.2.4)
- Urine pregnancy test (post-menarchal girls)
- Determination of the dose of a commercial basal insulin and mealtime insulin

As this visit ends the study on-treatment period, no more study medication will be dispensed and the investigator has to ensure that the patient continues with commercially available basal insulin as well as with mealtime insulin therapy. The choice of basal and mealtime insulin is at the discretion of the investigator/treating physician.

- Although decisions for transition dosing are ultimately those of the treating physician, it is suggested that a transition to an alternate form of basal insulin will be made by reducing the total daily dose of glargine by 20% for patients changing over from HOE901-U300 whereas patients receiving Lantus as the IMP will transition to a commercial basal insulin at the suggested 1:1 ratio (see Section 8.1.6).

Further adjustments of the insulin therapy during the 4-week post-treatment follow up period will be at discretion of the investigator/treating physician and will be documented in the e-CRF.

An appointment for the telephone Post-treatment Follow Up Visit 1 (Visit 19; two days [+2 days] later), and for the telephone Post-treatment Follow Up Visit 2 (Visit 20 – last study visit; four weeks ± 5 days after Visit 18) is given to the patient.

Patients who prematurely discontinue from the study treatment will be asked to attend all scheduled study visits and undergo study procedures until the planned end of treatment visit (or end of the 4-week post-treatment follow up period, whichever comes last); as a minimum, visit at Week 26/Visit 14 (assessments of primary and secondary efficacy endpoints) should be conducted. Such patients will not attend visit 19 and/or 20 if scheduled dates of these visits coincide with any of the scheduled visits until the planned end of study treatment (Week 52). During the planned end of treatment visit (Week 52) procedures related to the study drug normally scheduled for the End of treatment visit (eg, IVRS/IWRS contact for notification of end of treatment; collection of IMP pens, etc.) and already performed at the Early Treatment Discontinuation Visit will not be performed.

10.1.3 Post- treatment follow up period (the 4 weeks [± 5 days] following Visit 18)

After completion of the open-label randomized treatment phase, either scheduled or premature, patients enter the 4-week post-treatment follow up period where safety and insulin treatment data will be collected. The cost of the basal insulin as well as the mealtime insulin used during the 4-week post-treatment follow up period may be reimbursed if not covered by health insurance and if allowed by local regulations. During this period patients will perform SMPG measurements (see Section 9.1.2.2) and blood ketones measurements whenever applicable (see Section 10.6.2) and will record in the diary basal and mealtime insulin dosing data (see Section 9.1.2.3) as well as adverse events and hypoglycemia events, if any.

10.1.3.1 Post-treatment Follow up Visit 1 (Visit 19; two days [+2 days] after Visit 18) and Post-treatment Follow up Visit 2 (Visit 20 – End of Study Visit - four weeks [± 5 days] after Visit 18)

The patient/parent is called by the investigator or qualified designee at a scheduled time. If the call has been completed by site staff other than the investigator, the investigator has to be consulted if AE/SAE is suspected and informed in case AE/SAE occurred. A phone call visit can optionally be performed as a clinical visit.

During the phone call, answers to the following questions are to be obtained from the patient/parent:

- Did you experience any new medical event, disease or symptom since the last visit (please pay attention to any potential hypoglycemic events, potential allergic or injection site reaction)?
- Did you experience SMPG ≥252 mg/dL [14 mmol/L] while you were unwell (eg, you felt sick or nauseated; you had abdominal pain) or did you have persistent blood glucose values ≥252 mg/dL (14 mmol/L) without substantial decline over a period of approximately 60-120 min after injection of an extra dose of your rapid-acting insulin analogue, or were you ill with fever and/or vomiting? If yes, did you measure and record the level of blood ketones?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?

- Did you document your basal insulin and fast-acting insulin doses since the previous visit in the diary (see Section 9.1.2.3)?
- Data entered by the patient in the diary are reviewed (basal and mealtime insulin dose, SMPG values [see Section 9.1.2.2], hypoglycemia events, blood ketone values [see Section 10.6.2]).

The visits will also include:

- Record in the e-CRF names of commercial basal and mealtime insulins
- Document in the e-CRF AE/SAE, if any
- Arrange return of the diary and, if mandatory by local regulations, glucose meter and blood ketone meter (in case of premature treatment discontinuation the devices will be collected during the planned end of treatment visit – Week 52 [or at the end of the 4-week post-treatment follow up period, whichever comes last]).

10.2 DEFINITION OF SOURCE DATA

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

- Agreement and signature of informed consent form provided by the parent mentioning the study identification, as well as written assent or documentation of oral assent obtained from the patient as applicable,
- Patient and parent identification, patient's last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology,
- Previous and concomitant medication (including basal and mealtime insulin),
- IVRS/IWRS confirmation notifications by fax or e-mail (screening, screen failure, randomization, treatment reallocation, treatment/study discontinuation, treatment replacement if applicable, etc.),
- Study identification,
- Treatment kit number of IMP,
- Dates and doses of study medication administration (IMP and NIMP),
- Names of preparations and administration regimen of basal and mealtime insulin before and after study treatment,
- Dates of visits and assessments including the examination report,
- Vital signs, height, body weight, Tanner puberty stage signed and dated,
- Date and time of blood samples for PK analysis,
- Central laboratory reports and original report received at site,
- Adverse events and follow-up,
- In case of SAE, the site should file in the source documents at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE,

- Date of premature study discontinuation (if any) and reason,
- All relevant information collected during the investigator's call following hypoglycemic event or following patient's reporting of symptoms suggesting such event,

Source documentation may be found in the following:

- Patient's medical records (eg, discharge notes)
- Nursing notes
- Dietician's notes
- Physician's notes,
- Patient's diary
- Laboratory reports

10.2.1 Source data verification requirements for patients not randomized

For patients not randomized, the source data that must be checked include the patient's and parent's identification details, the informed consent signed by the parent, written assent or documentation of oral assent obtained from the patient as applicable, the study identification, the dates of study visits and the main reasons preventing randomization.

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

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

10.3.1 Temporary treatment discontinuation with investigational medicinal products

Temporary treatment discontinuation may be considered by the investigator because of suspected AEs. Re-initiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the investigator will have considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, ie, any day without IMP administration, patients are asked to report in their diary for IMP a dose 0 units for each of these days. Investigator will check patients´ diaries and ensure all days corresponding to a temporary treatment discontinuation are appropriately captured in the database. Additionally, the investigator must record in the e-CRF any non-study basal insulin administered as a replacement for IMP during those periods (see Section 8.9).

Temporary treatment (IMP) discontinuation decided by the investigator corresponds to one or more dose not administered to the patient.

10.3.2 Permanent treatment discontinuation with investigational medicinal product

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

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they/their parents decide to do so, at any time and irrespective of the reason, or this may be the investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF. Particular attention should be paid whether or not treatment discontinuation was associated with an adverse event or hypoglycemia and, if applicable, corresponding event has to be reported in the e-CRF.

The following will lead to permanent treatment discontinuation:

- Patient's own request or patient's parent request, ie, withdrawal of the consent for treatment
- If, in the investigator's opinion, continuation with the administration of IMP would be detrimental to the patient's well-being,
- Specific request of the Sponsor.
- Intercurrent condition that requires discontinuation of IMP: eg, laboratory abnormalities (see decision tree and general guidance for the follow up of laboratory abnormalities in Appendix C),
- The need to initiate the prohibited therapy (see Section 8.9.2)
- Pregnancy in all cases
- If, in the investigator's opinion, a female patient undertakes behavior deemed to be at risk of getting pregnant or decides to attempt to become pregnant.

Any abnormal laboratory value or electrocardiogram (ECG) parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

As soon as possible after the premature and permanent discontinuation of study treatment, the patients will be assessed using the procedure normally planned for the last day of the treatment period (Visit 18, Week 52, see Section 10.1.2.4). The 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 to evaluate insulin dose after switch-back to a non-study therapy during the initial four weeks after change over from the study treatment. As a minimum, visit at Week 26/Visit 14 (assessments of primary and secondary efficacy endpoints) should be conducted.

All cases of permanent treatment discontinuation should be recorded by the investigator in the appropriate pages of the e-CRF when considered as confirmed. IVRS/IWRS will be notified when a patient prematurely discontinues treatment.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients and their parents will be told that they are free to withdraw from the study at any time without any adverse effect on their care. However, if they no longer wish to take the IMP, they will be encouraged to remain in the study and attend the remaining visits or, at the minimum, attend Visit 14 at Week 26. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study. Patients who do not wish to continue in the study after the premature and permanent discontinuation of study treatment should be assessed as soon as possible after IMP discontinuation using the procedures normally planned for the End of Treatment visit (Visit 18, see Section 10.1.2.4).

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

For patients who fail to return to the study site for the End of Treatment visit, unless the patient withdraws the consent for follow-up, the investigator should make the best effort to re-contact the patient/parent (eg, contacting patient's parents or other member of family whose contact details were collected at the beginning of the study, or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. These contacts attempts must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients who withdraw (and/or their parents) should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient (and/or the parent) should withdraw consent in writing and, if the patient or the parent refuses or is physically unavailable, the site should document and sign the reason for the patient's or parent's failure to withdraw consent in writing. All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

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

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

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

- Results in death, or
- Is life-threatening, or

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 x ULN (upper limit of normal range) + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality

- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study, including in-situ malignancies
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.4.1.3 Adverse event of special interest

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

The AESIs are listed below:

- Symptomatic overdose with IMP/NIMP
  - A symptomatic overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the investigator or spontaneously notified by the patient/parent (not based on systematic drug accountability) and defined as follows:
    - any IMP or fast-acting mealtime insulin analogue (NIMP) dose administration which, in the investigator's opinion based on clinical judgment is considered significantly greater than the prescribed dose of insulin and which results in symptomatic hypoglycemia, ie, an event accompanied by clinical symptoms that are considered to result from low blood glucose regardless whether or not plasma glucose was determined. The event is treated with oral carbohydrate, glucagon or IV glucose.
  - Symptomatic overdose with IMP/NIMP (non-serious as well as serious) will be recorded on the standard AE form as "symptomatic overdose with IMP (or NIMP) accidental (or intentional)" and as hypoglycemia on the Hypoglycemia form. AE Safety Complementary form has to be completed, if serious.

  Of note, asymptomatic overdose (ie, an event defined as above but which does not result in clinical symptoms regardless whether or not plasma glucose was determined) has to be reported as a standard AE as "asymptomatic overdose with IMP (or NIMP) accidental (or intentional)". For asymptomatic IMP/NIMP overdoses events with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L), corresponding hypoglycemia has to be reported on Hypoglycemia form, too.
- ALT increase as outlined in flowchart in Appendix C.
- Pregnancy
  - Pregnancy will be recorded as an AE in all cases. It will be qualified as an SAE only if it fulfills SAE criteria.
  - In the event of pregnancy, study treatment should be discontinued and the sponsor informed immediately (ie, within 24 hours).
  - Follow-up of the pregnancy will be mandatory until the outcome has been determined.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or NIMPs or by the study procedure(s).
- Whenever an event resulted from another, separate event (eg, arm fracture secondary to fall), both should be reported separately.
- The investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant

medications, patient status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

A back-up plan (using a paper Case Report Form [CRF] process) is available and should be used when the e-CRF system does not work (see Appendix D).

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

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines (see Section 10.4.3), even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

Instructions for AE reporting are summarized in Table 2.

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix C.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal failure
- Suspicion of rhabdomyolysis

10.4.6 Summary of adverse event and hypoglycemia reporting instructions

See Table 2.

Table 2 - Summary of adverse event and hypoglycemia reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion			
			AE form	AE Safety Complementary Form	Hypoglycemia Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE, AESI or hypoglycemia	Yes	No	No	No
Hypoglycemia (non-SAE; non-AESI)	Routine	Any hypoglycemia that is not SAE or AESI	No	No	Yes	No
Serious Adverse Event (non-AESI; non-hypoglycemia)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No	No
Serious hypoglycemia (non-AESI)	Expedited (within 24 hours)	Any hypoglycemia meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	Yes	No
Adverse Event of Special Interest (non-SAE)	Expedited (within 24 hours)	Symptomatic overdose (see Section 10.4.1.3)	Yes	No	Yes	No
		ALT increase[1]	Yes	No	No	Yes
		Pregnancy	No	No	No	Yes
Adverse Event of Special Interest (serious)	Expedited (within 24 hours)	Symptomatic overdose (see Section 10.4.1.3)	Yes	Yes [2]	Yes	No
		ALT increase[1]	Yes	Yes	No	Yes
		Pregnancy	Yes	Yes	No	Yes
Laboratory, vital sign, or ECG abnormality recorded as AE (non- SAE, non-AESI)	Routine	Neutropenia, Thrombocytopenia, Acute renal failure, Rhabdomyolysis, Hyperglycemia with ketosis, Other	Yes	No	No	No

Footnote:
[1] See criteria defined in Appendix C
[2] Corresponding to the overdose adverse event and to the related severe hypoglycemia event

10.5 OBLIGATIONS OF THE SPONSOR

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

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, Institutional review boards/ Independent ethics committees (IRBs/IECs) as appropriate and to the investigators.
- All SAEs that are expected and at least reasonably related to the IMP to the regulatory authorities, according to local regulations.

In this study, some AEs considered related to the underlying condition (eg, blood glucose increased) will not be considered unexpected as given in the Investigator's Brochure.

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

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypoglycemia instructions

Symptoms suggestive of hypoglycemia will be explained to patients/parents as well as situations posing the patient at high risk of hypoglycemia. Patients/parents will be instructed to measure finger stick plasma glucose levels with the study-provided glucose meter prior to the administration of carbohydrates whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose rescue prior to confirmation, and then a glucose measurement should be performed as soon as safe, with appropriate diary documentation.

Additional information related to the hypoglycemic event will be collected in the diary as soon after the event as possible. Following severe events, patients/parents will contact the sites as soon as possible to review the details and decide on any necessary measures to be taken.

Patients will report in the diary the occurrence of symptoms suggesting hypoglycemia with or without SMPG values. Patients with SMPG value ≤70 mg/dL (3.9 mmol/L) will document in the diary whether it was symptomatic or asymptomatic. If symptomatic, appropriate hypoglycemic symptoms will be reported. In all cases, patients/parents will document whether severity of symptoms warranted assistance in the patient's care.

All hypoglycemia episodes will be documented by the study site on the "hypoglycemia specific form" in the e-CRF. This includes all symptomatic hypoglycemia events and asymptomatic hypoglycemia. Hypoglycemia events fulfilling the criteria of an SAE including all hypoglycemia events associated with coma, seizure or unconsciousness will be documented on the "hypoglycemia specific form" and as SAE on the "Adverse Event" form (category "Serious

Hypoglycemia") with corresponding complementary forms (AE Safety Complementary Form) in the e-CRF (see Table 2, Summary of adverse event and hypoglycemia reporting instructions).

For instructions concerning symptomatic hypoglycemia event resulting from an overdose with the IMP/NIMP, see Section 10.4.1.3 and Table 2.

Categories of hypoglycemia which will be assessed are described in Section 9.2.1.

10.6.2 Hyperglycemia with ketosis instructions

Testing of capillary ketones must be performed using the meter provided by the sponsor:

- When SMPG is ≥252 mg/dL (≥14 mmol/L) in an unwell child (eg, feeling sick or nauseated; persistent polyuria, abdominal pains, rapid breathing)
- When SMPG persists at ≥252 mg/dL (≥14 mmol/L) without substantial decline over a period of approximately 60-120 minutes after injection of an extra dose of rapid-acting insulin analogue
- During illness with fever and/or vomiting

Ketone readings 1.5 mmol/L or more and concomitant SMPG ≥252 mg/dL (14 mmol/L) will be considered as alert for development of diabetic ketoacidosis and the investigator will be contacted immediately. The event will be reported as AE or – if respective criteria are met – as SAE (see Section 10.4.1.2). Self-measured ketones values will be documented in the diary.

10.6.3 Local tolerability at injection site and hypersensitivity reactions

If the investigator or the patient/parent recognizes any signs of local intolerability at the site of IMP or NIMP injection or hypersensitivity reactions, the event should be recorded in the adverse event page in the e-CRF. For local reactions at IMP/NIMP injection site, the event verbatim will include localization and, if known, the insulin (IMP or NIMP) associated with the reaction.

If a patient reports severe injection site or hypersensitivity reaction between the on-site visits or during a phone call visit, the investigator should ask him/her to come to the study site on the same or the next day, so that the event can be properly assessed, reported and treated. Severe injection site reactions should be photographed if possible.

10.6.4 Follow-up of laboratory abnormalities

Decision trees for the management of specific laboratory abnormalities are provided in Appendix C.

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the primary efficacy variable of HbA1c change from baseline to 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% HbA1c 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 nQuery Advisor® Software Version 7.0.

11.1.1 Justification of the non-inferiority margin

Previous randomized studies in Type 1 diabetes involving Lantus were considered for the justification of the choice of non-inferiority margin: in studies of similar duration, with HbA1C as the primary endpoint, and designed to show superiority of Lantus versus NPH human insulin, the sample size calculation was based on a mean expected difference between treatment groups ranging between 0.5% and 0.7%. In study 4010 (a 30-week randomized study comparing Lantus and NPH in combination with insulin lispro), superiority of Lantus over NPH was shown, with an estimated difference in HbA1C change between Lantus and NPH of -0.53% (95%CI: -0.93, -0.13). To be in line with recommendations by regulatory agencies (11, 12) and considering that the non-inferiority margin must be less than the effect of Lantus versus NPH, and that the experimental treatment (HOE901-U300) is requested to preserve a notable fraction of the effect considered as clinically relevant, a non-inferiority margin of 0.3% was considered appropriate, corresponding to preservation of around 50% of a difference ranging between 0.5% and 0.7%.

11.2 DISPOSITION OF PATIENTS

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

- Screened: all patients who originally met inclusion criteria and signed the informed consent form;
- Screen failure patients and reason for screen failure;
- Randomized: all screened patients with a treatment arm allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not;
- Safety population (Section 11.3.2), presented as treated;
- The intent-to-treat (ITT) population (Section 11.3.1.1 analyzed as randomized);

- The randomization strata (Age group at screening visit [<12 years and ≥12 years] and screening HbA1c categories [<8.5%, ≥8.5%]) 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;
- Completed populations (presented as randomized):
  - Patients who have completed the main 6-month on-treatment period (who have performed Visit 14 (Month 6/ Week 26)) and who did not permanently discontinue treatment;
  - Patients who completed the main 6-month randomized period (patients who have performed visit 14);
  - Patients who have completed the 12-month on-treatment period (who have performed Visit 18 (Month 12/ Week 52)) and who did not permanently discontinue treatment;
  - Patients who completed the 12-month randomized period (patients who have performed visit 18);
- Patients who permanently discontinued the IMP during the main 6-month treatment period, and the reasons for permanent treatment discontinuation;
- Patients who did not complete the main 6-month randomized period;
- Patients who discontinued the main 6-month randomized period by main reason for study discontinuation;
- Patients who permanently discontinued the IMP during the 12-month treatment period, and the reasons for permanent treatment discontinuation;
- Patients who did not complete the 12-month randomized period;
- Patients who discontinued the 12-month study by main reason for randomized discontinuation.

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

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

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

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

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

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent–to-treat population

The primary efficacy population will be the ITT population, which includes all randomized patients, analyzed according to the treatment group allocated by randomization.

11.3.2 Safety population

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

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

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

- If a patient is dispensed IMP and is lost to follow-up without any documented evidence whether or not the patient took IMP, the patient will be considered exposed and included in the safety population.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.

In addition:

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

11.3.3 PK population

All patients who provided at least one PK measurement and who do not have major deviation regarding administration of IMP will be included in the PK population.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

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

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

(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.

11.4.1.2 Daily insulin doses

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

11.4.1.3 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.

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

11.4.2 Analyses of efficacy endpoints

Efficacy analyses will be performed on the ITT population.

All efficacy parameters will be summarized by treatment group for each visit and at endpoint for the main 6-month randomized period and the 12-month randomized period respectively.

11.4.2.1 Analysis of primary efficacy endpoint

11.4.2.1.1 Primary analysis

The primary efficacy variable (change in HbA1c from baseline to Month 6 in % as defined in Section 9.1.1) will be analyzed for non-inferiority assessment, in the ITT population using all post-baseline HbA1c data available up to Month 6, regardless of study treatment discontinuation (analysis on the main 6-month randomized period (defined in Section 9.1), 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 administration 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 parts, are provided below:

1. 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 administration treatment group as predictor. Missing data will be imputed using the regression method.
2. Missing data in patients who complete the main 6-month on-treatment period will be imputed separately, using a model estimated from data observed in other patients who complete the main 6-month on-treatment period and have change in HbA1c available at Week 26. The imputation model will include the administration treatment group, the randomization stratum of age group at screening visit (<12 years and ≥12 years), the continuous fixed covariates of baseline HbA1c value, as well as the change from baseline in HbA1c observed at Week 12. Since in general, the missing pattern will not be monotone, a two-step approach will be used:
    - Step 1: the Markov Chain Monte Carlo (MCMC) method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern.

- Step 2: using the monotone data set from step 1, missing data will be imputed using the regression method.

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 administration treatment group, randomization strata, as well as the continuous fixed covariates of baseline 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 Month 6 for both treatment groups, as well as, the differences of these estimates, with their corresponding standard errors (SEs) and 95% CIs.

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

- Step 1: 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%.
- Step 2: only if the previous step of the hierarchical procedure has been demonstrated, superiority of HOE901-U300 over Lantus in HbA1c change from baseline to endpoint (Month 6) 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 Month 6 between HOE901-U300 and Lantus is <0.

The tests for the primary endpoint (Month 6) will be performed one-sided at level $\alpha = 0.025$.

11.4.2.1.2 Key sensitivity analysis

A sensitivity analysis will be performed on the change in HbA1c from baseline to Month 6 on patients who complete the main 6-month on-treatment period in the ITT population, (ie, patients who perform Visit 14 [Week 26] and who do not permanently discontinue treatment). A similar multiple imputation approach as described for primary analysis part 2 will be used (ie, for missing data in patients who complete the main 6-month on-treatment period).

11.4.2.1.3 Sensitivity analyses to handle missing data

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

Penalized multiple imputation (MI)

In order to assess the impact of missing data, the change in HbA1c from baseline to Month 6 in % using HbA1c values during the randomized 6-month period (all post baseline available data), will be analyzed in the ITT population using a multiple imputation approach to account for missing

data at any time points (including missing baseline, Week 12 and Month 6) followed by the testing of treatment arms using an analysis of covariance (ANCOVA) model.

Missing data will be imputed 1,000 times to generate 1,000 complete data sets with the MI SAS procedure. For each simulation leading to negative imputed value, another value will be redrawn for imputation using MINIMUM option of multiple imputation SAS procedure. Since in general, the missing pattern will not be monotone, a two-step approach will be used:

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

The imputation model for step 1 will include the treatment group, baseline HbA1c value, as well as HbA1c values at Week 12 and Month 6.

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

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

The imputed HbA1c value at Week 26 in the HOE901-U300 group will then be penalized by adding 0.3% (corresponding to the non-inferiority margin) to the imputed HbA1c value whereas the imputed HbA1c in the Lantus group will not be penalized. The change in HbA1c from baseline to endpoint will then be derived from observed and imputed (penalized or not) HbA1c value at Week 26.

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

Tipping point analysis

In order to assess the impact of missing data, a tipping-point analysis based on the pattern mixture model approach will also be performed. A specific illustration on the value of the minimum penality leading to a non-rejection of the null hypothesis will be provided (13).

The tipping point analysis will be conducted by multiply imputing missing HbA1c values with a delta adjustment in the HOE901-U300 arm. In the tipping point analysis, missing HbA1c values at Week 26 will be imputed and a delta (HbA1c increase) will be added to each imputed value in the HOE901-U300 arm in the ITT population.

To investigate how the conclusions depend on the adopted values of delta, the testing will be repeated over a range of plausible values for delta. Results will be then summarized using graphs.

Further pattern mixture models could be explored depending on the observed missing data pattern in the HOE901-U300 arm.

11.4.2.2 Analyses of secondary efficacy endpoints

Secondary efficacy endpoints are described in Section 9.1.2.

All secondary efficacy endpoints will be analyzed and summarized on the main 6-month randomized period using the ITT population (ITT estimand).

Secondary efficacy endpoints will be analyzed in the ITT population, using all available data on the 6-month randomized period (ITT estimand).

A similar multiple imputation approach in two parts, as described above for the primary efficacy endpoint, adding randomization stratum of screening HbA1c (<8.5%; ≥8.5%) only in part 2 imputation model (ie, for missing data in patients who complete the main 6-month on-treatment period), will be used for change from baseline in FPG at Week 26. This analysis will be used descriptively.

The other continuous secondary endpoints will be analyzed descriptively only.

Categorical efficacy parameters 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. 95 % confidence interval for the treatment difference or ratios will be provided for descriptive purpose only.

All secondary endpoints will be evaluated at end of treatment of the whole study (Week 52), for descriptive purpose, using the same statistical methods as described above.

11.4.2.3 Multiplicity considerations

To control the type I error, a hierarchical step-down testing procedure will be applied.

- Step 1: non-inferiority comparison of the mean change from baseline to Month 6/ Week 26 in HbA1c with HOE901-U300 compared to Lantus
- Step 2: 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 other secondary efficacy variables will be analyzed for exploratory purpose only.

11.4.3 Analyses of safety data

Safety endpoints are described in Section 9.2.

The summary of safety results will be presented by treatment group for the main 6-month TEAE period in the 6-month CSR and for the 12-month TEAE period (as defined in Section 9.2) in the 12-month CSR.

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

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

The following definitions will be applied to laboratory parameters, vital signs and ECG:

- 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 and vital signs.
- PCSA criteria will determine which patients had at least one PCSA during the TEAE periods, taking into account all evaluations performed during the TEAE periods, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage during the TEAE periods.

11.4.3.1 Hypoglycemia

Incidence of patients with at least one hypoglycemia event will be presented by type of event and treatment group, during the TEAE periods.

Number and rate of hypoglycemia event per patient-year will be summarized by type of event and treatment group, during the TEAE periods.

Incidence of patients with at least one hypoglycemia event and number of hypoglycemia events per patient-year will be also presented by treatment period (titration phase, maintenance phase, over 26 weeks of treatment and over 52 weeks of treatment).

Hypoglycemia episodes of the categories defined in Section 9.2.1 will be analyzed:

- by diurnal distribution (0:00-23:59);
- 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-up the patient 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);

- by treatment periods: 6-month TEAE period, 12-month TEAE period, from first injection of IMP to end of week 8, from start of week 9 to month 6, monthly rates;
- by HbA1c, by age range and by Tanner puberty stage.

11.4.3.2 Hyperglycemia with ketosis

Incidence of patients with at least one hyperglycemia with ketosis event will be presented by type of event and treatment group, during the TEAE periods.

Number and rate of hyperglycemia with ketosis event per patient-year will be summarized by type of event and treatment group, during the TEAE periods.

Incidence of patients with at least one hyperglycemia with ketosis event and number of hyperglycemia with ketosis events per patient-year will be also presented by treatment period (titration phase, maintenance phase, over 26 weeks of treatment and over 52 weeks of treatment).

11.4.3.3 Adverse events

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.

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

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

<u>Death</u>

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

- Number (%) of patients who died by study period (TEAE periods, on-study, post-study) and reasons for death summarized by treatment received
- Death in nonrandomized patients or randomized and not treated patients

TEAE leading to death (death as an outcome on the AE e-CRF page as reported by the investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

<u>Injection site reaction and hypersensitivity reaction</u>

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

Adverse event of special interest

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

11.4.3.4 Laboratory safety 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) by treatment group for the TEAE periods.

The incidence of PCSAs at any time during the TEAE periods 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 parameter for which no PCSA criterion is defined, similar table(s) using the normal range is provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP, 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.

Listing of possible Hy's Law cases identified will be provided by treatment group (eg, patients with any elevated ALT ≥3xULN, and associated with an increase in bilirubin >2xULN (ULN) with: ALT, AST, ALP, Total bilirubin and the following complementary parameters (if available): Conjugated Bilirubin and Prothrombin Time / INR ,CPK, serum creatinine, complete blood count.

11.4.3.5 Vital signs and physical examination

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables (values and changes from baseline) including body weight, height, BMI, will be calculated for each visit or study assessment (baseline, each post baseline time point, last on-treatment) by treatment group for the TEAE periods. The Tanner puberty stage data will be summarized too.

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

11.4.3.6 Analyses of AIA variables

The analyses of AIA data are performed based on the safety population.

AIA analyses will be detailed in the Statistical Analysis Plan.

11.4.4 Analyses of pharmacokinetic variables

PK data analysis will be performed using a population PK approach. Details of such analysis will be documented in a separate analysis plan.

11.5 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 6-month comparative treatment period. The timing of this analysis is when the last randomized patient has completed the 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.

11.6 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 (extension by further 6 months).

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

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

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

12.2 INFORMED CONSENT

The investigator (according to applicable regulatory requirements), or a person designated by the investigator, should fully inform the patient (and the parent[s]) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the ethics committee (IRB) /(IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the informed consent form should be signed, name filled in and personally dated by the patient's parent(s) or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. Local law must be observed in deciding whether 1 or both parents consent is required. If only 1 parent signs the consent form, where both signatures are required, the investigator must document the reason for only 1 parent signature.

In addition, participants will assent as detailed below or will follow the Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center.

Patients who can read the assent form will do so before writing their name and dating and signing the form.

Patients who cannot read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given. Such patients, if only are able to write, will also be offered to sign and date the form.

The informed consent form and the assent form used by the investigator for obtaining the Parent´s informed consent and Patient´s assent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

The same rules apply to the consent for optional PK blood sampling, including assent process with the patient.

Prior to collection of blood for PK evaluations, the optional PK informed consent form (written) must be signed, name filled in, and personally dated by the parent(s), and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the parent. The optional PK assent form must be obtained from the patient prior to collection of blood for PK evaluations, according to the rules applicable to the main study assent.

The main study informed consent form and the optional PK informed consent forms as well as corresponding assents used by the investigator for obtaining the parent's informed consent as well as the patient's assent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

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

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

In relation with the population of patients exposed in the trial ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

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

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

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATORS

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the e-CRF entries against the source documents, except for the pre-identified source data directly recorded in the e-CRF. The informed consent form will include a statement by which the parent allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records of the patient which support the data on the e-CRFs (eg, patient's medical file, patient's diary entries, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

It is the responsibility of the investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. In case of a need to use back-up plan for SAE and other investigator Expedited Events reporting process eg, due to e-CRF system failure, all CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

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

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

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

13.5 USE OF COMPUTERIZED SYSTEMS

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

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

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

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

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

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

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

14.3 CONFIDENTIALITY

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

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

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

Patients’ race or ethnicity (eg, "Caucasian/white, Black, Asian/Oriental, others") will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for Food and Drug Administration, on Japanese population for the PMDA in Japan).

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

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

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and to provide a summary of study results to the investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

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

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