NCT05413369

STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, 24 weeks, active-controlled, open-label, 2-arm multicenter study comparing the efficacy and safety of iGlarLixi to IDegAsp in Chinese type 2 diabetes mellitus participants suboptimally controlled with oral antidiabetic drug(s)**
Protocol number:	**LPS17396**
Compound number (INN/Trademark):	**HOE901/AVE0010 iGlarLixi/Soliqua®**
Study phase:	**Phase 3**
Short Title:	**iGlarLixi vs IDegAsp in Chinese participants on OAD(s)** SoliD – (Soliqua – iGlarLixi in Chinese patients after OAD[s])
Statistician:	[redacted]
Statistical project leader:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for study LPS17396 is based on the amended protocol 01 dated 16 June 2022. There are no major changes to the statistical analysis features in this SAP.

The first participant was randomized on 18 July 2022.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	14-Nov-2023	For the other secondary endpoint "total insulin dose in each group at Week 24", estimand attributes were added in this SAP.	The details of estimand were not defined in protocol. Estimand attributes were added following team's decision.

1 INTRODUCTION

There are no major changes to the analyses described in the protocol.

1.1 STUDY DESIGN

- Open-label, 1:1 randomized, active-controlled, 2 treatment-arm, 24-week treatment duration, parallel-group, multicenter phase 3 study
- Participants with type 2 diabetes mellitus (T2DM) treated with metformin ± one additional oral antidiabetic drug (OAD) would be recruited in this study.
- The randomization will be stratified by value of screening HbA1c (<8%, ≥8%), and by use at screening of metformin alone or metformin + SGLT-2i (Yes/No), ie, by oral antidiabetic treatment use at screening (metformin ± SGLT-2i / metformin + OAD other than SGLT-2i). The overall objective of this last stratification group is to ensure that participants who will need to discontinue their second OAD are well balanced between groups
- Total duration of study participation for each participant is up to 27 weeks.
- This study comprises of 3 periods:
  - An up-to 2-week screening period during which: a sulfonylurea (SU), a glinide, an alpha-glucosidase inhibitor (alpha-GI), or a dipeptidyl-peptidase-4 (DPP-4) inhibitor, if previously taken, will be discontinued. Sodium-glucose co-transporter 2 (SGLT-2) inhibitor, if previously taken, will be kept at the stable dose; metformin treatment will maintain at the stable dose (at least 1000 mg/day or a maximal tolerated dose).
  - A 24-week, open-label randomized treatment period with iGlarLixi or IDegAsp, both on top of metformin ± SGLT-2 inhibitor.
  - A 3-day post-treatment safety follow-up period.
- Screening is from signed informed consent to randomization.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate the non-inferiority of iGlarLixi versus IDegAsp on glycated hemoglobin A1c (HbA1c) change from baseline to Week 24	• Change in HbA1c from baseline to Week 24
Key secondary efficacy	
• To demonstrate superior therapeutic effect of iGlarLixi versus IDegAsp on HbA1c and body weight change, proportion of participants at	• 2a Change in HbA1c from baseline to Week 24 • 2b Change in body weight from baseline to Week 24

Objectives	Endpoints
HbA1c target, proportion of participants at target without weight gain and/no hypo after 24 weeks of treatment	• 2c Proportion of participants to reach HbA1c<7% at week 24 • 2d Proportion of participants reaching HbA1c targets <7% without body weight gain at Week 24 • 2e Proportion of participants reaching Hba1c <7% with no body weight gain at Week 24 and no hypoglycemia (defined as ADA level 1,2 or 3) during treatment
Other secondary	
• To further assess the therapeutic effect of iGlarLixi in comparison with IDegAsp on other glycemic control parameters after 24 weeks of treatment • To assess total insulin dose and percentage of participants requiring rescue therapy over the 24 weeks treatment	• Change in fasting plasma glucose from baseline to Week 24 • Change in 7-point self-monitored plasma glucose (SMPG) profile from baseline to Week 24 (each time point and average daily value) • Proportion of participants reaching HbA1c target <7% at Week 24 with no hypoglycemia (defined as ADA level 1, 2 or 3) during treatment • Proportions of participants reaching HbA1c target <7% at Week 24 with no clinically relevant hypoglycemia (defined as ADA level 2 or 3) during treatment • Total insulin dose in each group at Week 24 • Percentage of participants requiring rescue therapy during the 24-week treatment period • Change in fasting C-peptide from baseline to Week 24
Secondary Safety	
• To assess safety and tolerability of iGlarLixi versus IDegAsp	• Incidence and event rates of hypoglycemia (Any, ADA classification level 1, 2, and 3) • Adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs),and AEs leading to treatment discontinuation, vital signs and safety laboratory values

1.2.1 Estimands

Primary estimand defined for main endpoints are summarized in below Table 2. More details are provided in Section 3.

For all these estimands, the comparison of interest will be the comparison of iGlarLixi vs. IDegAsp.

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To demonstrate the non-inferiority of iGlarLixi versus IDegAsp on glycated hemoglobin A1c (HbA1c) change from baseline to Week 24				
Primary endpoint (Primary estimand)	Change in HbA1c from baseline to Week 24[a]	All randomized participants	Treatment policy strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	LS Means difference between treatments. Multiple imputation of missing data using missingness patterns based on treatment completion, and under the missing at random (MAR) assumption within each pattern.
Primary endpoint (Secondary estimand 1)	Change in HbA1c from baseline to Week 24[a]	All randomized participants	Hypothetical strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	LS Means difference between treatments. Missing data handled by mixed-effect model with repeated measures (MMRM) under MAR assumption.
Primary endpoint (Secondary estimand 2)	Change in HbA1c from baseline to Week 24[a]	Per Protocol	No intercurrent event expected as participants with treatment discontinuation or rescue medication will be excluded from PP population	LS Means difference between treatments. No missing data handling method is planned for this analysis.
Key secondary efficacy objective: To demonstrate superior therapeutic effect of iGlarLixi versus IDegAsp on HbA1c and body weight change, proportion of participants at HbA1c target, proportion of participants at target without weight gain and/no hypo after 24 weeks of treatment				

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Key secondary efficacy endpoint (Primary estimand)	Change from baseline to Week 24 in: • HbA1c[b] • Body weight	All randomized participants	Treatment policy strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	LS mean difference between treatments. Multiple imputation of missing data using missingness patterns based on treatment completion, and under the MAR assumption within each pattern.
	If a participant achieves: • HbA1c < 7% at Week 24 • HbA1c < 7% and no body weight gain at Week 24 • HbA1c < 7% and no body weight gain at Week 24 and no hypoglycemia (defined as any hypoglycemia ADA level 1. 2 or 3) during treatment	All randomized participants	Treatment policy strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	Odds ratio between treatments. If no assessment is available at Week 24, participants will be treated as non-responders.
Key secondary efficacy endpoint (Secondary estimand)	Change from baseline to Week 24 in: • HbA1c[b] • Body weight	All randomized participants	Hypothetical strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	LS Means difference between treatments. Missing data handled by MMRM under MAR assumption.
Other secondary objectives: To further assess the therapeutic effect of iGlarLixi in comparison with IDegAsp on other glycemic control parameters after 24 weeks of treatment. To assess total insulin dose and percentage of participants requiring rescue therapy over the 24 weeks treatment				
Other secondary endpoints (Primary estimand)	Change from baseline to Week 24 in: • FPG • 7-point SMPG • Fasting C-peptide	All randomized participants	Treatment policy strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	LS mean difference between treatments. Multiple imputation of missing data using missingness patterns based on treatment completion, and under the MAR assumption within each pattern.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
	If a participant achieves: • HbA1c < 7% at Week 24 and no hypoglycemia (any hypoglycemia ADA level 1. 2 or 3) during treatment • HbA1c < 7% at Week 24 and no clinically relevant hypoglycemia (any hypoglycemia ADA level 2 or 3) during treatment	All randomized participants	Treatment policy strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	Odds ratio between treatments. If no assessment is available at Week 24, participants will be treated as non-responders.
	If a participant initiates rescue medication by Week 24	All randomized participants	Treatment policy strategy for intercurrent event: • Treatment discontinuation[c]	Odds ratio between treatments. If no assessment is available at Week 24, participants will be treated as non-responders.
	Total insulin dose in each group at Week 24	All randomized participants	Treatment policy strategy for intercurrent event: • Initiation of rescue medication Hypothetical strategy for intercurrent event: • Treatment discontinuation	LS Means difference between treatments. Missing data handled by mixed-effect model with repeated measures (MMRM) under MAR assumption.

a For noninferiority testing.
b For superiority testing.
c Initiation of rescue medication is not applicable for this estimand.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 3 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Per-protocol (PP)	All participants from ITT population who have completed 24 weeks of randomized treatment and did not start any rescue therapy before end of the 24-week randomized treatment period and have no major or critical protocol deviation that can potentially affect efficacy analysis. The protocol deviations for PP exclusion are defined in Section 5.7 and will be confirmed and finalized for each patient prior to the database lock. Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who have taken at least 1 dose of study intervention, regardless of the amount of treatment administered. Participants will be analyzed according to the intervention they actually received.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety/population as randomized.

For any participant randomized more than once, only the data associated with the first randomization (except if the first randomization is done by error) will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the intervention group as randomized if the participant received at least one administration as randomized.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first injection of open label investigational medicinal product (IMP). For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

Unless otherwise specified, analyses will be performed by intervention group (and overall for baseline and demographics characteristics).

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first injection of open-label IMP.
- The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first injection of open-label IMP to the last injection of IMP + 3 days (1 day for hypoglycemia).
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

3.2.1 Definition of endpoint(s)

The primary endpoint is the absolute change from baseline to week 24 in HbA1c. All the efficacy assessments collected during the study will be used, including those obtained after treatment discontinuation or initiation of rescue therapy (refer to Section 5.5 for definition).

3.2.2 Main analytical approach

The null and the alternative hypotheses based on non-inferiority margin of 0.3% are described as:

H_0: iGlarLixi – IDegAsp $\geq$ 0.3% versus H_a: iGlarLixi – IDegAsp < 0.3%

If the upper bound of the two-sided 95% confidence interval for the difference of iGlarLixi – IDegAsp is smaller than 0.3%, the study will be considered to have met its primary objective and the non-inferiority of iGlarLixi over IDegAsp is established.

The primary endpoint will be analyzed with the primary estimand defined according to the following attributes:

- Endpoint: Change in HbA1c from baseline to Week 24.
- Treatment condition: iGlarLixi will be compared to IDegAsp.
- Analysis population: All randomized participants
- Intercurrent events (IE):
  - Treatment discontinuation IE will be handled with the treatment policy strategy: the endpoint will be assessed based on all assessments irrespective of the treatment discontinuation
  - The initiation of rescue medication IE will be handled with the treatment policy strategy: the endpoint will be assessed based on all assessments irrespective of the initiation of rescue medication
- Population-level summary: LS Means difference between treatments from analysis of covariance (ANCOVA) with treatment groups and previous OADs as fixed effects, and baseline HbA1c continuous value as covariate. Standard errors (SE), 2-sided 95% confidence intervals (CI) and 2-sided non-inferiority p-value from ANCOVA will be provided. Missing data will be imputed by multiple imputations using missingness patterns based on treatment completion, and under the missing at random (MAR) assumption within each pattern.
  - For participants completing the 24-week treatment period, the missing HbA1c values will be imputed using data from other participants completing the treatment.
  - For participants discontinuing prematurely the treatment, the missing HbA1c values will be imputed using data from participants also discontinuing treatment but having their HbA1c assessment (retrieved dropouts). In case there are not enough observed Week 24 data post treatment discontinuation, ie, less than 10 in either arm, or the model does not converge, whichever happens, return-to-baseline (RTB) approach will be used for imputation; missing HbA1c values at Week 24 will be imputed from a normal distribution with the expected value set to the participant's baseline value and standard deviation based on the baseline value by treatment group.

Missing HbA1c values will be imputed 1000 times to generate 1000 datasets with complete HbA1c values using SAS procedure for multiple imputation (PROC MI). The imputation model will include the treatment group as fixed effect, and baseline, Week 8, Week 12 and Week 18 HbA1c continuous value as covariate. The randomization stratum of HbA1c can be removed from the model given that the baseline HbA1c continuous value is already in the model.

For each of the 1000 imputed datasets, the change in HbA1c from baseline to Week 24 will be analyzed using an ANCOVA with treatment groups and previous OADs as fixed effects, and baseline HbA1c continuous value as covariate. The results obtained from analyzing the datasets will be combined using Rubin's rule to draw inference.

The non-inferiority will be assessed using the upper bound of the 2-sided 95% confidence interval (CI). If the upper bound of the 95% CI is less than 0.3%, the non-inferiority of iGlarLixi versus IDegAsp will be claimed.

Descriptive statistics for HbA1c results and changes from baseline will be provided for baseline and each visit by treatment group. Mean changes from baseline with the corresponding standard error will be plotted over time.

Missing data assumption check

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

- To explore missing data patterns for HbA1c in the primary efficacy analysis, number (%) of participants and number (%) of participants by baseline characteristics will be presented by the following missing data pattern and by treatment group. Descriptive statistics and plots for HbA1c results and changes from baseline will be provided by missing data pattern and by treatment group:
  - Pattern 1: participants who have completed treatment and have Week 24 HbA1c value,
  - Pattern 2: participants who have completed treatment and do not have Week 24 HbA1c value,
  - Pattern 3: participants who have not completed treatment and have Week 24 HbA1c value,
  - Pattern 4: participants who have not completed treatment and do not have Week 24 HbA1c value.
- Baseline characteristics and HbA1c values by visit will be presented by missing data pattern for each treatment group, using descriptive statistics and/or graphs.
- Further exploratory analyses will be performed to evaluate factors influencing missing data: for each baseline characteristic, a logistic regression will be performed to model the missingness (Yes, No) at Week 24. The model will include fixed-effect terms for treatment group, the categorical fixed-effect term or continuous fixed covariate of the studied baseline characteristic and the interaction between treatment group and covariate studied. Estimates and p-value will be provided for descriptive purpose. A separate model will be run for each baseline characteristic. Additional multivariate analyses may be performed if needed.

3.2.3 Sensitivity analysis

- The primary estimand will be analyzed using a MMRM, under the missing at random framework. The model will include treatment, previous OADs, visit (Week 8, Week 12 and Week 18), treatment-by-visit interaction as fixed effects, and baseline HbA1c value-by-visit interaction as continuous covariate. The randomization stratum of HbA1c will be removed from the MMRM model given that the baseline HbA1c value is already in the model. The MMRM model will be implemented using SAS® (Version 9.4 or higher) MIXED procedure (PROC MIXED) with an unstructured correlation matrix to model the

within-participant errors. Parameters will be estimated using the restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degree of freedom will be estimated using the Kenward-Roger approximation by fitting values from post-randomization visits. LS Means difference between treatments, SE, 2-sided 95% CI, and 2-sided non-inferiority p-value from MMRM will be provided.

- The analysis of primary estimand will be repeated under a penalized multiple imputation strategy based on ITT population. The imputed HbA1c value at Week 24 in the iGlarLixi group will be penalized by adding 0.3% (corresponding to the non-inferiority margin), whereas the imputed HbA1c in the IDegAsp group will not be penalized.

3.2.4 Supplementary analyses

Secondary estimand 1

Under hypothetical strategy, measurements after treatment discontinuation and/or initiation of rescue medication will be considered as missing data.

A MMRM, under the missing at random framework, will be performed based on ITT population. The model will include treatment, previous OADs, visit (Week 8, Week 12, Week 18 and Week 24), treatment-by-visit interaction as fixed effects, baseline HbA1c value-by-visit interaction as continuous covariate. The randomization stratum of HbA1c will be removed from the MMRM model given that the baseline HbA1c continuous value is already in the model. The MMRM model will be implemented using SAS® (Version 9.4 or higher) MIXED procedure (PROC MIXED) with an unstructured correlation matrix to model the within-participant errors. Parameters will be estimated using the restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degree of freedom will be estimated using the Kenward-Roger approximation by fitting values from post-randomization scheduled visits. LS Means difference between treatments, SE, 2-sided 95% CI, and 2-sided nominal non-inferiority p-value from MMRM will be provided.

Secondary estimand 2

For the per protocol estimand, the change in HbA1c from baseline to Week 24 will be analyzed using an ANCOVA with treatment group and previous OADs as fixed effects, and baseline HbA1c continuous value as covariate. Provided that participants with treatment discontinuation or rescue medication, as well of participants with missing assessment will be excluded from PP population, no missing data handling method is planned for this analysis. LS Means difference between treatments, SE, 2-sided 95% CI, and 2-sided nominal non-inferiority p-value from ANCOVA will be provided.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are key secondary efficacy endpoints and other secondary efficacy endpoints. Secondary safety endpoints analyses are defined in Section 3.6.2 (AE, SAE, AESIs, AEs leading to treatment discontinuation, hypoglycemia), and Section 3.6.3.1 (vital signs, safety laboratory values).

3.3.1 Key secondary efficacy endpoints

3.3.1.1 Definition of endpoints

The key secondary efficacy endpoints are:

- 2a The absolute change from baseline to week 24 in HbA1c.
- 2b The absolute change from baseline to week 24 in body weight.
- 2c Proportion of participants reaching HbA1c<7% at week 24.
- 2d Proportion of participants reaching HbA1c targets <7% without body weight gain at Week 24.
- 2e Proportion of participants reaching HbA1c <7% with no body weight gain at Week 24 and no hypoglycemia (defined as ADA level 1, 2 or 3) during treatment.

3.3.1.2 Main analytical approach

Key secondary efficacy endpoint 2a

If the primary objective is met, the key secondary efficacy endpoint 2a will be analyzed with the primary estimand defined the same as the primary estimand of the primary endpoint, except that 2-sided 97.5% CI and superiority p-value from ANCOVA will be provided if endpoint is to be tested as per the gate-keeping procedure defined in Section 3.5; otherwise, 95% CI will be provided and no p-value will be provided.

Key secondary efficacy endpoint 2b

The key secondary efficacy endpoint 2b will be analyzed with the primary estimand defined according to the following attributes

- Endpoint: Change in body weight from baseline to Week 24.
- Treatment condition: iGlarLixi will be compared to IDegAsp.
- Analysis population: All randomized participants
- Intercurrent events (IE):
  - Treatment discontinuation IE will be handled with the treatment policy strategy: the endpoint will be assessed based on all assessments irrespective of the treatment discontinuation
  - The initiation of rescue medication IE will be handled with the treatment policy strategy: the endpoint will be assessed based on all assessments irrespective of the treatment discontinuation
- Population-level summary: LS Means difference between treatments from ANCOVA with treatment group, randomization stratum of HbA1c and previous OAD and baseline body weight as covariates. SE, 2-sided 97.5% CI and superiority p-value from ANCOVA will be provided if endpoint is to be tested as per the gate-keeping procedure defined in

Section 3.5; otherwise, 95% CI will be provided and no p-value will be provided. Missing data will be imputed by multiple imputations using missingness patterns based on treatment completion, and under the missing at random (MAR) assumption within each pattern. The same imputation method as of the primary estimand of the primary endpoint will be used.

Descriptive statistics for body weight and changes from baseline will be provided for baseline and each visit by treatment group. Mean changes from baseline with the corresponding standard error will be plotted over time.

Key secondary efficacy endpoint 2c, 2d, and 2e

The key secondary efficacy endpoints 2c, 2d, and 2e will be analyzed with the primary estimand defined according to the following attributes:

- Treatment condition: iGlarLixi will be compared to IDegAsp.
- Analysis population: All randomized participants
- Intercurrent events (IE):
  - Treatment discontinuation IE will be handled with the treatment policy strategy: the endpoint will be assessed based on all assessments irrespective of the treatment discontinuation
  - The initiation of rescue medication IE will be handled with the treatment policy strategy: the endpoint will be assessed based on all assessments irrespective of the initiation of rescue medication
- Population-level summary: Odds ratio between treatments from logistic regression model adjusting for treatment group, randomization stratum of previous OADs, and appropriate baseline covariates. The proportion of participants in each treatment group will be provided, as well as the odds ratio between groups (HbA1c and body weight will be included as baseline continuous covariates when considered in the definition of endpoints). If an endpoint is to be tested as per the gate-keeping procedure defined in Section 3.5, 2-sided CI at the specified significance level and the associated p-value will be provided; otherwise, 95% CI will be provided and no p-value will be provided. For the categorical secondary endpoints in which HbA1c is assessed at Week 24, all values at Week 24 will be used to determine whether a participant is a responder or not, even if they are measured after IMP discontinuation or introduction of rescue therapy. If no assessment is available at Week 24, participants will be treated as non-responders.

3.3.1.3 Supplementary analysis

Secondary estimands of key secondary efficacy endpoints 2a and 2b

Under hypothetical strategy, measurements after treatment discontinuation and/or initiation of rescue medication will be considered as missing data.

A MMRM, under the missing at random framework, will be performed for the secondary estimands of both key secondary efficacy endpoints 2a and 2b. The model will include treatment, randomization stratum of HbA1c, randomization stratum of previous OADs, visit, treatment-by-visit interaction as fixed effects, appropriate baseline value and baseline-by-visit interaction as continuous covariate. For the analysis of HbA1c, the randomization stratum of HbA1c will be removed from the MMRM model given that the baseline HbA1c continuous value is already in the model. The MMRM model will be implemented using SAS® (Version 9.4 or higher) MIXED procedure (PROC MIXED) with an unstructured correlation matrix to model the within-participant errors. Parameters will be estimated using the restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degree of freedom will be estimated using the Kenward-Roger approximation by fitting values from post-randomization scheduled visits. LS Means difference between treatments, SE, 2-sided 97.5% CI, and 2-sided superiority p-value from MMRM will be provided if endpoint is to be tested as per the gate-keeping procedure defined in Section 3.5; otherwise, 95% CI will be provided and no p-value will be provided.

3.3.2 Other secondary endpoints

3.3.2.1 Definition of endpoints

The other secondary endpoints are:

- Change in fasting plasma glucose from baseline to Week 24
- Change in 7-point self-monitored plasma glucose (SMPG) profile from baseline to Week 24 (each time point and average daily value)
- Proportion of participants reaching HbA1c target <7% at Week 24 with no hypoglycemia (defined as ADA level 1, 2 or 3) during treatment
- Proportions of participants reaching HbA1c target <7% at Week 24 with no clinically relevant hypoglycemia (defined as ADA level 2 or 3) during treatment
- Total insulin dose in each group at Week 24, defined as the sum of the insulin dose in U and U/kg from IMP and NIMP (eg, rescue therapy).
- Percentage of participants requiring rescue therapy during the 24-week treatment period
- Change in fasting C-peptide from baseline to Week 24

3.3.2.2 Main analytical approach

The other secondary endpoints of will be analyzed with the primary estimand defined according to the following attributes:

- Treatment condition: iGlarLixi will be compared to IDegAsp.
- Analysis population: All randomized participants for all endpoints, and additionally safety population for total insulin dose.
- Intercurrent events (IE):

- For total insulin dose in each group at Week 24
  - Treatment discontinuation IE will be handled with the hypothetical strategy: the endpoint will be considered as missing after treatment discontinuation
  - The initiation of rescue medication IE will be handled with the treatment policy strategy: the endpoint will be assessed based on all assessments irrespective of the initiation of rescue medication
- For percentage of participants requiring rescue therapy during the 24-week treatment period
  - Treatment discontinuation IE will be handled with the treatment policy strategy: the endpoint will be assessed based on all assessments irrespective of the treatment discontinuation
- For other endpoints:
  - Both treatment discontinuation IE and initiation of rescue medication IE will be handled with the treatment policy strategy: the endpoint will be assessed based on all assessments irrespective of the IE

- Population-level summary:
  - For change in FPG, 7-point SMPG and fasting C-peptide from baseline to Week 24: LS Means difference between treatments from ANCOVA with the same analysis approach as of the primary estimand of the primary endpoint, except that the baseline of each endpoint will be included in the model rather than baseline HbA1c. Descriptive statistics for results and changes from baseline will be provided for baseline and each visit by treatment group. Mean changes from baseline with the corresponding standard error will be plotted over time. For 7-point SMPG, the average and each time point will be analyzed.
  - For total insulin dose in each group at week 24: LS mean difference between treatments, as well as SE and 2-sided 95% CI, from MMRM with treatment, randomization stratum of HbA1c, randomization stratum of previous OADs, visits and treatment-by-visit interaction as fixed effects. Descriptive statistics for percentage change from starting dose will be provided. Raw data and changes from starting dose with the corresponding standard error will be plotted over time.
  - For binary endpoints: Odds ratio between treatments from logistic regression model adjusting for treatment group, randomization stratum of previous OADs, baseline continuous HbA1c and appropriate baseline covariates. The proportion of participants in each treatment group will be provided, as well as the odds ratio between groups with associated 2-sided 95% CI. For the categorical secondary endpoints in which HbA1c is assessed at Week 24, all values at Week 24 will be used to determine whether a participant is a responder or not, even if they are measured after IMP discontinuation or introduction of rescue therapy. If no assessment is available at Week 24, participants will be treated as non-responders.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

Not applicable.

3.5 MULTIPLICITY ISSUES

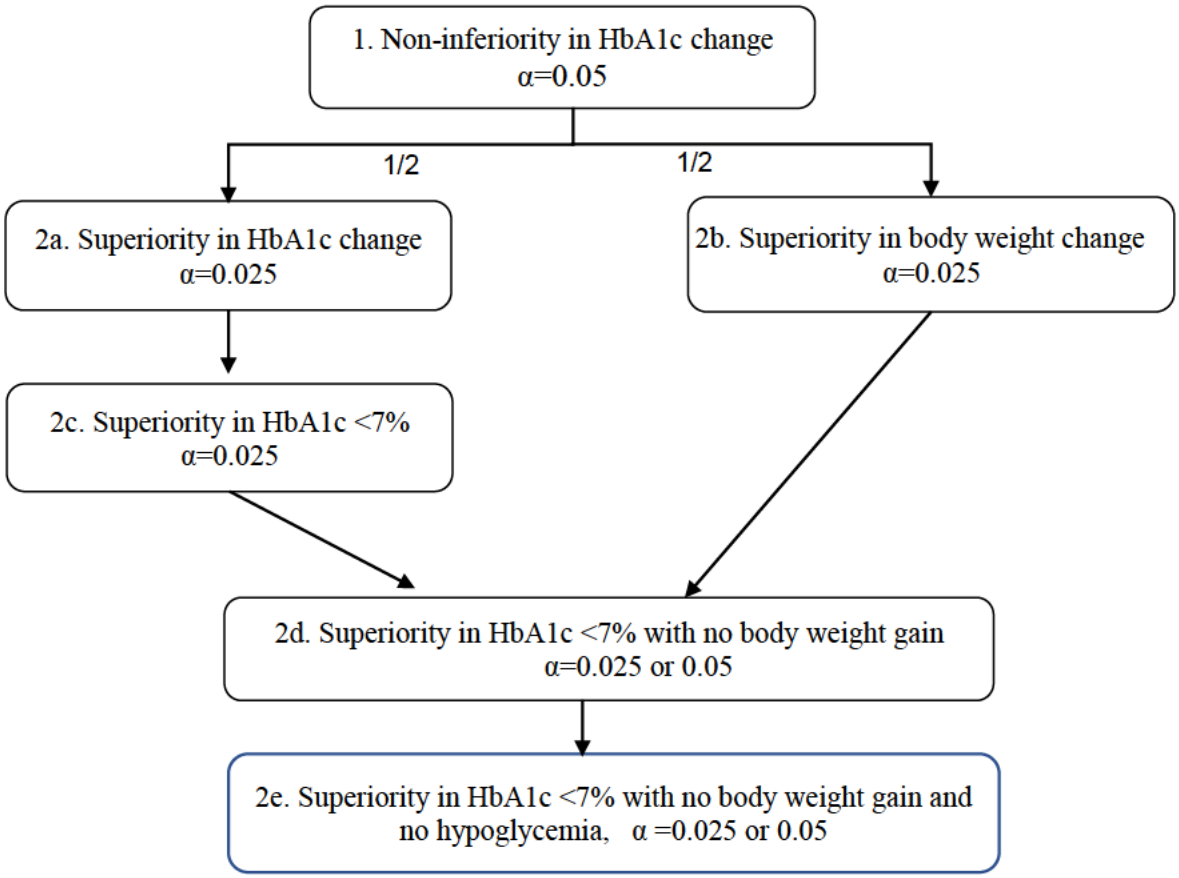
Multiplicity adjustment: to control overall Type I error at 0.05 level (2-sided), a gate-keeping procedure will be used. Two families of hypothesis testing will be established: family 1 of primary and family 2 of key secondary hypotheses. For the primary endpoint (change from baseline to Week 24 in HbA1c), no multiplicity adjustment is needed to control the Type I error since only one comparison of iGlarLixi versus IDegAsp will be performed.

If the primary endpoint is statistically significant at the 2-sided 0.05 level, a hierarchical testing procedure will be performed to test the following key secondary efficacy endpoints in the order specified in Figure 1.

- Superiority in 2a and 2b will be test at the 2-sided 0.025 level each.
- Only if 2a is statistically significant, 2c will be tested at the 2-sided 0.025 level.
- 2d will be tested at the 2-sided 0.05 level if both 2b and 2c are statistically significant, or at the 2-sided 0.025 level if only one of them is statistically significant.
- If 2d is statistically significant, 2e will be tested at the 2-sided 0.025 or 0.05 level based on the significant level passed from 2d.

This gate-keeping procedure will only apply for the primary analysis of the primary estimand for each endpoint. For other secondary hypotheses, no multiplicity adjustment will be applied.

Figure 1 - Graphical illustration of the gate-keeping procedure



3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2 , unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided.

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure is defined as: (Date of the last open-label IMP injection – Date of the first open-label IMP injection) + 1 day, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing. Duration of IMP exposure will be summarized quantitatively and categorically: 1 to 14, 15 to 28, 29 to 56, 57 to 84, 85 to 126, 127 to 160, 161 to 168, and > 168 days.

Additionally, the cumulative duration of treatment exposure (expressed in participant-years and defined as the sum of the duration of treatment exposure for all participants divided by 365.25) will be provided.

In both treatment groups, final insulin dose at the end of the open-label randomized treatment period will be summarized quantitatively and categorically: 1 to 10, >10 to 20, >20 to 30, >30 to 40, and >40 U. For iGlarLixi group, the final lixisenatide dose at the end of the open-label randomized treatment period will be summarized quantitatively and categorically: 1 to 10, >10 to 15, >15 to 20, and >20 µg.

Treatment compliance

Overall treatment compliance is defined as the actual number of days with IMP injection compared to the planned number of days with IMP injection during the open-label treatment period, up to treatment discontinuation. It will be calculated according to the following formula:

Compliance rate (%) = total number of days with IMP injection / planned number of days with IMP injection * 100.

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

Treatment compliance will be summarized quantitatively and categorically: <60%, ≥60% to <80%, ≥80% to ≤100%, and >100%.

3.6.2 Adverse events

General common rules for adverse events

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

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.

- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period regardless of initiation of rescue medication, ie, from the first injection of open-label IMP to the last injection of open-label IMP + 3 days (1 day for hypoglycemia).
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period, ie, 4 days (2 days for hypoglycemia) after last injection of open-label IMP to end of study.

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE. For the analysis of time to event, incomplete date of onset will be imputed to the earliest possible; after imputation, if the imputed date is earlier than the date of the first injection of IMP, it will be overwritten by date of the first injection of IMP.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. Missing intensity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 4.

Table 4 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the iGlarLixi intervention group.
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any treatment-emergent SAE
- Any TEAE leading to death
- Any TEAE leading to permanent treatment discontinuation

The AE summaries of Table 5 will be generated with number (%) of participants experiencing at least one event.

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HLGT, HLT and PT
	Primary SOC and PT
	Primary and secondary SOC, HLGT, HLT and PT
Common TEAE (≥1% in any group)	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAE	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC, HLGT, HLT and PT
TEAE leading to permanent treatment discontinuation	Primary SOC, HLGT, HLT and PT
	Primary SOC and PT
TEAE leading to death[a]	Primary SOC, HLGT, HLT and PT
	Primary SOC and PT
Pretreatment AE	Primary SOC and PT
Post-treatment AE	Primary SOC and PT
Post-treatment SAE	Primary SOC and PT

a Death as an outcome of the AE as reported by the Investigator in the AE page

Among all TEAEs, Kaplan-Meier curves will be provided, when appropriate, for the time to first onset of the following PTs: nausea, vomiting and diarrhea as appropriate.

The frequency of TEAEs over time will be provided for nausea, vomiting and diarrhea as appropriate, using weekly time intervals up to 24 weeks, ie, [0-1] week, (1,2] weeks, (2,3] weeks, (3,4] weeks, etc. In each time interval, the numerator in the calculation of percentages will be the number of participants with at least 1 TEAE occurring in this time interval. Two types of analyses will be included: (1) only the first event will be counted for each participant and all recurrent events will not be included, and the denominator for the calculation of percentages will be the number of participants at risk at the beginning of the time interval who did not experience a first event in the preceding intervals; graphical presentations will also be provided for the percentages of participants with nausea, vomiting and diarrhea as appropriate by week; and (2) the recurrent events in subsequent intervals will be counted once for each participant in the numerator of the corresponding interval, and the denominator for the calculation of percentages will be the number of participants at risk at the beginning of the time interval.

Analysis of deaths

In addition to the analyses of deaths included in Table 4 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods
- Deaths in non-randomized participants or randomized but not treated participants

Analysis of adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 6. Number (%) of participants experiencing at least one event will be provided for each event of interest, by primary SOC and PT if applicable. Tables will be sorted as indicated in Table 4.

Table 6 - Selections for AESIs

AESIs	Selection
• Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP. - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria. - In the event of pregnancy in a female participant, IMP should be discontinued. - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been. • Symptomatic overdose (serious or nonserious) with IMP/NIMP - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count). • Increase in alanine transaminase (ALT) more than 3 times the ULN	e-CRF specific tick box on the AE page

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets: hemoglobin, hematocrit, red blood cell count, platelet count, red blood cell indices (MCV, MCH, %Reticulocytes)
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils

- Clinical chemistry:
  - Metabolism: glucose, total protein, lipase, amylase
  - Electrolytes: sodium, potassium, calcium
  - Renal function: creatinine, creatinine clearance, eGFR, blood urea nitrogen, uric acid
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, total and direct bilirubin
  - Pregnancy test: urine human chorionic gonadotropin (hCG) (as needed for women of childbearing potential)
- Vital signs: heart rate, systolic and diastolic blood pressure in sitting position, and weight
- ECG variables: ECG assessments will be described as normal, abnormal and clinically significant (Y/N) if abnormal

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

Quantitative analyses

When relevant, for laboratory variables and vital signs above, descriptive statistics for results and changes from baseline will be provided for each visit, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable. For parameters defined as efficacy endpoints, PCSA summaries will not be provided.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either scheduled, nonscheduled or repeated).

For laboratory variables and vital signs above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

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

3.6.3.2 Analysis of hypoglycemia

Hypoglycemia events will be identified from e-CRF "Hypoglycemic Event Information". Analyses of hypoglycemia will be performed on events occurring during the on-treatment period and post-treatment period, including any hypoglycemia, level 1 hypoglycemia, level 2 hypoglycemia, level 3 hypoglycemia, hypoglycemia occurred on daytime, hypoglycemia occurred nocturnally, defined as:

- Any hypoglycemia event meeting ADA definition Level 1, Level 2, or Level 3.
- Level 1 hypoglycemia: a measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L).
- Level 2 hypoglycemia: a blood glucose concentration <54 mg/dL (3.0 mmol/L).
- Level 3 hypoglycemia: a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery, corresponding to e-CRF "Required Assistance Because Subject Was Not Capable of Helping Self" ticked for "Assistance Required?".
- Hypoglycemia occurred on daytime: on e-CRF page "Hypoglycemic Events" the "Time of Event" is between 6:00 to 23:59 (inclusive). An additional analysis will be performed for events with "Between Waking and Bedtime" ticked for "When did the Hypoglycemic Event occur?".
- Hypoglycemia occurred nocturnally: on e-CRF page "Hypoglycemic Events" the "Time of Event" is between 0:00 to 5:59 (inclusive). An additional analysis will be performed for events with "Between Bedtime and Waking" ticked for "When did the Hypoglycemic Event occur?".

The number (n) and incidence rate (%) of participants experiencing at least one specific hypoglycemic event will be summarized by treatment group. Each hypoglycemic endpoint will be analyzed using a logistic regression model adjusting for treatment group, randomization strata of HbA1c and previous OADs and appropriate baseline covariates. The proportion of participants in each treatment group will be provided, as well as the odds ratio between groups with associated 2-sided 95% CI. Level 1 hypoglycemia and Level 2 hypoglycemia during on-treatment period will be analyzed further by symptoms (symptomatic or asymptomatic) with the same methodology.

The hypoglycemic event rate per participant year will be derived for each type of hypoglycemia and will be summarized by treatment group. A negative binomial model will be fitted in SAS to estimate the event rate. The number of hypoglycemic events is the response variable. The independent variables will be treatment group, randomization strata of HbA1c and previous OADs used as fixed effects and appropriate baseline covariates. The logarithm of the duration (in years) of open-label randomized treatment period as an offset variable to account for unequal follow-up time due to early withdrawal, rescue medication, etc. The ratio of hypoglycemic events rate and it's 2-sided 95% CI will be presented. The estimated mean hypoglycemic events in two groups along with their 95% CIs are presented from this model.

The pattern of symptomatic hypoglycemia occurrence over time will also be assessed, if appropriate. The number (%) of participants with at least 1 symptomatic hypoglycemia with blood glucose concentration <70 mg/dL (3.9 mmol/L) during the on-treatment period will be assessed over time, using weekly time intervals up to 24 weeks, ie, [0-1] week, (1-2] weeks, (2-3] weeks, (3-4] weeks, etc. In each time interval, the numerator in the calculation of percentages will be the number of participants with at least 1 event occurring in this time interval. Two types of analyses will be performed: (1) only the first event will be counted for each participant and all recurrent events will not be included, and the denominator will be the number of participants at risk at the beginning of the time interval who did not experience a first event in the preceding intervals; and (2) the recurrent events in subsequent intervals will be counted once for each participant in the numerator of the corresponding interval, and the denominator will be the number of participants at risk at the beginning of the time interval.

A Kaplan-Meier curve will also be provided for the time to first symptomatic hypoglycemia with blood glucose concentration <70 mg/dL (3.9 mmol/L) during the on-treatment period.

The number (%) of participants with at least 1 symptomatic hypoglycemia with blood glucose concentration <70 mg/dL (3.9 mmol/L) during the on-treatment period, as well as the corresponding number of events, will be summarized as necessary by hour of the day for each treatment group, using the following hour intervals: ≥23:00 to <06:00, ≥06:00 to <10:00, ≥10:00 to <14:00, ≥14:00 to <18:00, ≥18:00 to <23:00.

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

Not applicable.

3.7.2 Subgroup analyses

Depending on the data availability (categories with fewer than 5 participants may be combined with other categories), subgroup analyses will be performed on the primary endpoint to summarize the treatment effects across subgroups defined by the following baseline or screening factors:

- Age group (<50, ≥50 to <65, ≥65 to <75, ≥75 years).
- Sex (Male, Female).
- Baseline BMI level (<24, ≥24 to <28, ≥28 kg/m2).
- Randomization stratum of screening HbA1c (<8%, ≥8%).
- Randomization stratum of oral antidiabetic use at screening (Metformin ± SGLT-2i / Metformin + other OAD).
- Baseline fasting C-peptide level by quartiles.

The same imputed datasets for primary analysis will be used for the subgroup analyses. Treatment-by-subgroup interaction term and the subgroup factor term will be added in the primary model. In the case that the subgroup factor is identical or similar to a randomization stratum factor, the stratum factor will not be kept in the model.

The treatment effects (iGlarLixi versus IDegAsp) for the primary endpoint will be provided, as well as the corresponding 95% CI, for each subgroup, and the interaction p-value, using the same method as applied to the primary analysis of primary estimand. Forest plots will be provided.

3.8 INTERIM ANALYSES

No formal interim analysis for efficacy or safety is planned for this study.

4 SAMPLE SIZE DETERMINATION

A total sample size of 580 participants (randomization ratio 1:1, ie, 290 per intervention group) will be determined to demonstrate noninferiority of iGlarLixi versus IDegAsp in HbA1c reduction at Week 24 with 90% power and 2-sided significance level of 0.05 based on the following assumptions on the primary endpoint:

- True mean difference of zero between iGlarLixi and IDegAsp
- Common standard deviation of 1.05%
- Non-inferiority margin on the mean difference of 0.3%
- Dropout rate of 10%

Calculations were made based on two sample t-test using SAS® (Version 9.4).

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
AESIs:	adverse events of special interest
BMI:	body mass index
ECG:	electrocardiogram
HGLT:	high level group term
HLT:	high level term
ITT:	intent-to-treat
LLT:	lower-level term
MAR:	missing at random
MedDRA:	medical dictionary for regulatory activities
MMRM:	mixed-effect model with repeated measures
OAD:	oral antidiabetic drug
PCSA:	potentially clinically significant abnormality
PT:	preferred term
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SGLT-2:	sodium-glucose co-transporter 2
SOC:	system organ class
TEAE:	treatment-emergent adverse event
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants
- Participants who completed the study treatment period as per protocol

- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation
- Participants who completed the study period as per protocol
- Participants who did not complete the study period as per protocol and main reason for study discontinuation.

The number of exposed and not randomized participants will also be summarized.

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

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and diabetes history will be summarized using descriptive statistics in the randomized population.

Demographic and baseline characteristics

- age in years as quantitative variable and in categories (<50, ≥50 to <65, ≥65 to <75, ≥75)
- gender (Male, Female)
- race (Asian)
- baseline body mass index (BMI) in kg/m^2 as quantitative variable and in categories (<24, ≥24 to 28, ≥28)
- randomization stratum of screening HbA1c (<8%, ≥8%)
- randomization stratum of oral antidiabetic use at screening (Metformin ± SGLT-2i, Metformin + other OAD)

Baseline efficacy characteristics

- HbA1c % as quantitative variable
- body weight in kg as quantitative variable
- fasting plasma glucose in mmol/L as quantitative variable

- 7-point SMPG in mmol/L as quantitative variable in daily average
- fasting C-peptide level in nmol/L as quantitative variable and by quartiles

Baseline safety will be presented along with the safety summaries.

General medical/surgical history will be collected. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Diabetes history

- Duration of type 2 diabetes in years derived as: (Date of informed consent – Date of diagnosis of diabetes + 1)/365.25
- Age at onset of diabetes in years derived as: Year of diagnosis of diabetes – Year of birth
- Duration of prior metformin treatment in years derived as: (Date of informed consent - Date of first intake of metformin + 1)/365.25
- Baseline daily dose metformin in mg as quantitative variable and in categories (<1000, ≥1000 to <1500, ≥1500 to <2500, ≥2500)
- Prior use of SGLT-2i (Yes, No)
- Duration of prior SGLT-2i treatment in years derived as: (Date of informed consent – Date of first intake of SGLT-2i + 1)/365.25
- Prior use of OADs other than metformin or SGLT-2i (Yes, No)
- Duration of prior OADs other than metformin or SGLT-2i in years derived as: (Date of informed consent - Date of first intake of OAD + 1)/365.25
- Gestational diabetes
- Diabetic retinopathy
- Diabetic neuropathy
- Diabetic nephropathy
- Creatinine clearance at baseline in mL/min/1.73m^2 as quantitative variable and in categories (<30, ≥30 to < 60, ≥60 to <90, ≥ 90)

In case of partial date of diagnosis of diabetes and date of first intake of metformin/SGLT-2i/other OADs, the date will be imputed only for the derivation of diabetes history as follows:

- If only year is available, it will be imputed as July 1st.
- If year and month are available, it will be imputed to the 15th day.

Prior or concomitant medications

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

- Prior medications are those the participant received prior to first injection of IMP. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP during the on-treatment period.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior, concomitant and post-treatment medications will be summarized for the randomized population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

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

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Analysis windows for HbA1c and body weight

The following analysis windows will be used to decide how the scheduled and/or unscheduled visits will be used in the analyses of efficacy variables: HbA1c and body weight.

A measurement (scheduled or unscheduled, central or local, pre-rescue and premature end of treatment) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

The analysis window for HbA1c and body weight is given below.

Table 7 - Analyses window definition for HbA1c and body weight

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 4 (Visit 6)	28	1 to 41
Week 8 (Visit 8)	56	42 to 69
Week 12 (Visit 10)	84	70 to 104
Week 18 (Visit 12)	126	105 to 146
Week 24 (Visit 14)	168	≥147

Study days are calculated considering Day 1 as the day of the first injection of open label IMP (or the day of randomization for participant not exposed).

Analysis windows for other endpoints

For safety parameters and efficacy parameters other than HbA1c and body weight, unscheduled, pre-rescue and premature end of treatment assessments will be reallocated to the closest scheduled visit per the schedule of assessment only if the scheduled assessment is missing with the rules defined below:

- Lower bound = targeted day of current scheduled visit - integer part of (targeted day of current scheduled visit – targeted day of the preceding scheduled visit)/2;
- Upper bound = targeted day of current scheduled visit + integer part of (targeted day of the next scheduled visit – targeted day of current scheduled visit -1)/2;
- Lower bound for the first scheduled post-baseline visit is always Day 1 (the day of first IMP injection);
- No upper bound is specified for the last scheduled post-baseline visit.

Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will be used for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits.

5.5 APPENDIX 5 DEFINITION AND MEDICAL ALGORITHM FOR "RESCUED PARTICIPANTS" / RESCUE MEDICATION USE

Participants who meet one of the following conditions will be considered as "rescued":

- In the eCRF page "Medications", if there is any medication with "Rescue Therapy" ticked for "Reason for Treatment".
- In the eCRF page "Medications", if there is no medication with "Rescue Therapy" ticked for "Reason for Treatment" and the participant meets any of the criteria in medical algorithm for rescued participants, defined as below.

Medical algorithm for rescued participants

- Short/rapid-acting insulin is given for > 10 days continuously, or ≤ 10 days continuously if it occurs within 2 weeks prior to the last HbA1c measurement.
- New OAD is taken in addition to metformin+/- SGLT-2i (identified from eCRF page "Medications") > 10 days continuously, or ≤ 10 days continuously if it occurs within 2 weeks prior to the last HbA1c measurement.
- The dose of background therapy is increased for > 10 days continuously, or ≤10 days continuously if it occurs within 2 weeks prior to the last HbA1c measurement.

Nevertheless, the participants must not be considered rescued if:

- The date of anti-diabetic initiation is on or after the date of last IMP injection.
- The date of anti-diabetic initiation is before Week 12.
- The anti-diabetic medication was taken due to IMP unavailability during COVID-19 pandemic.

5.6 APPENDIX 6 CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013;165(4):489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	
QTc	Absolute values (ms) >450 ms >480 ms >500 ms Increase from baseline Increase from baseline]30-60] ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.

5.7 APPENDIX 7 PRE-DEFINED PROTOCOL DEVIATIONS AND CATEGORIZATION

Category for Protocol Deviation* *(severity)* *(DVCATINI)*	Protocol Deviation Coded Term* *(DVDECOD)*	Deviation Number* *(DVSPID)*	Protocol Deviation Term* *(DVTERM)*	Inclusion/ Exclusion criterion number *(IETESTCD)*	Inclusion/Exclusion from PPS
CRITICAL	Informed consent procedures	0101	Study Informed consent/ Assent form never obtained for the study and personal data collected or intervention(s) performed	N/A	Exclude
CRITICAL	Informed consent procedures	0104	Study Informed consent/Assent form not obtained for an amendment requiring a re-consent	N/A	Exclude
MAJOR	Inclusion/Exclusion criteria	0201	Participant must be at least 18 of age inclusive, at the time of signing the informed consent.	I01	Exclude
MAJOR	Inclusion/Exclusion criteria	0202	Participants who are diagnosed with T2DM for at least 1 year before the screening visit	I02	Exclude if less than 11 months; Include otherwise
MAJOR	Inclusion/Exclusion criteria	0203	Treated for >= 3 months prior to the visit 1 with a stable dose of metformin (>= 1000 mg/day or the MTD) alone or plus a second oral antidiabetic treatment	I03	Include if >= 90 days; Exclude otherwise
MAJOR	Inclusion/Exclusion criteria	0204	HbA1c at visit 1: 7.5% to 11%, if treated with metformin +/- SGLT-2 inhibitor, or 7.0% to 10%, if treated with metformin + a 2nd OAD other than SGLT-2 inhibitor.	I04	Exclude
MAJOR	Inclusion/Exclusion criteria	0206	Body mass index (BMI) <40 kg/m2 at screening	I06	Exclude case by case during PD review before DBL
MAJOR	Inclusion/Exclusion criteria	0235	Previous treatment with insulin (except for short-term treatment =<14 days due to intercurrent illness at the discretion of the Investigator) within 1 year prior to screening.	E05	Exclude

Category for Protocol Deviation* *(severity) (DVCATINI)*	Protocol Deviation Coded Term* *(DVDECOD)*	Deviation Number* *(DVSPID)*	Protocol Deviation Term* *(DVTERM)*	Inclusion/ Exclusion criterion number *(IETESTCD)*	Inclusion/Exclusion from PPS
MAJOR	Inclusion/Exclusion criteria	0236	Use of oral or injectable glucose-lowering agents other than those stated in the inclusion criteria within 3 months prior to screening.	E06	Exclude
MAJOR	Inclusion/Exclusion criteria	0237	Use of systemic glucocorticoids (excluding topical application or inhaled forms) for 1 week or more within 3 months prior to screening.	E07	Exclude case by case during PD review before DBL
MAJOR	Inclusion/Exclusion criteria	0238	Use of weight loss drugs within 3 months prior to screening.	E08	Exclude
MAJOR	Inclusion/Exclusion criteria	0240	Use of any investigational drug other than specified in this protocol within 1 month or 5 half-lives, whichever is longer, prior to screening.	E10	Exclude
MAJOR	Concomitant Medications/ Therapy	0301	NIMP not administered	N/A	Exclude case by case during PD review before DBL
MAJOR	Concomitant Medications/ Therapy	0303	Protocol prohibited therapy/medication/vaccine/ administered	N/A	Exclude
MAJOR	IMP Management	0501	IMP not administered	N/A	Exclude based on automatic PD
MAJOR	Randomization procedure	0605	IMP kit number actually dispensed to the participant is different from the IMP kit number allocated	N/A	Exclude if IMP treatment number doesn't correspond to the IMP allocated per randomization process (ie, participant switched from treatment group).