NCT05413369

AMENDED CLINICAL TRIAL PROTOCOL 01

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**
Amendment number:	**01**
Compound number: (INN/Trademark):	**HOE901/AVE0010** **iGlarLixi/Soliqua®**
Brief title:	**iGlarLixi vs IDegAsp in Chinese participants on OAD(s)**
Acronym:	**SoliD – (Soliqua – iGlarLixi in Chinese patients after OAD[s])**
Study phase:	**Phase 3**
Sponsor name:	
Monitoring team's representative name and contact information	
Regulatory agency identifier number(s):	

IND:	Not applicable
EudraCT:	Not applicable
NCT:	Not applicable
WHO:	U1111-1267-2772
EUDAMED:	Not applicable
Other:	Not applicable

Date: 16-June-2022 Total number of pages: 100

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	All	16 June 2022, version 1 (electronic 2.0)
Original Protocol	All	14 Sept 2021, version 1 (electronic 1.0)

Amended protocol 01 (16 June 2022)

This amended protocol 01 (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment (01) is intended to support further evaluation of the therapeutic effect of iGlarLixi on ß-cell function in the study population. In addition to the primary objective to demonstrate the non-inferiority of iGlarLixi versus IDegAsp (Ryzodeg 70/30) on glycemic control, an additional secondary outcome is included to assess the status of ß-cell function after 24 weeks of treatment with iGlarlixi versus iDegAsp, which could provide evidence of the effect of the evaluated treatment on ß-cell function. Additionally, assessment of ß-cell function at baseline will allow to evaluate clinical outcomes with iGlarlixi vs IDegAsp in subgroup population according to baseline ß-cell functionality.

C-peptide is a widely used measure of pancreatic ß-cell function. It will be evaluated at the baseline (Visit 2/Week 0) and at the end of the treatment (Visit 14/Week 24). Correspondingly, the change in fasting C-peptide from baseline to Week 24 will be added into the “other objective and endpoints” for statistical analyses.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page and throughout	Document title updated to "Amended Clinical Trial Protocol 01".	Title page amendments added as per Sanofi standards.
	Updated Amendment information.	
	Protocol Amendment Summary of changes, including, document history, Overall rationale for the amendment and protocol amendment summary of changes table, added.	
	Added "Acronym: SoliD (Soliqua – iGlarLixi in Chinese patients after OAD[s])"	An acronym is available for the study.
	Updated all other formatting, reference orders, header, etc, relating to protocol amendment, and corrected any formatting inconsistencies.	Formatting updated throughout as per Sanofi standards.
Section 1.1 Synopsis Section 3 Objectives and Endpoints	"Change in fasting C-peptide from baseline to Week 24" was added to "Other secondary endpoints".	To add an additional endpoint for the assessment of the "other secondary objective".
Throughout the document	Capitalize the i in IDegAsp.	Consistency.
Section 1.3 Schedule of Activities (SOA)	Added "Fasting C-peptide" to "Central Laboratory test" with check-marks X at Visit 2/Week 0, and Visit 14/Week 24.	Measurement of fasting C-peptide at Visit 2 and Visit 14 by central lab for assessment of the additional endpoints.
	"FPG" was transferred in a separate row. "X" was added to Visit 2.	FPG will be measured also at randomization as a reference for IMP starting dose.
	Footnote "m Participants must be in fasting status, not have any food and drinks (except for water) for at least 8 hours" was added.	The samples for measurement of C-peptide and FPG should be collected at the fasting state.
	Footnote "n Fasting C-peptide sample at Visit 14/Week 24 should be only collected for participants who have C-peptide samples collected at Visit 2/Week0" was added.	Clarification that paired samples (baseline/end of study) of fasting C-peptide are needed for endpoint analysis.
	Fasting C-peptide: Added "X" in the E/D column.	Fasting C-peptide will be measured in case of E/D.
	Footnote i: Added "in any two days in the week prior to the visit. Participants should be reminded to perform the 7-point SMPG profile or, the onsite visit should be postponed allowing for the performances".	Clarification that the 7-point SMPG profile must be completed before the onsite visit.

Section # and Name	Description of Change	Brief Rationale
Section 3.1 Appropriateness of measurements	"ß-cell function will be assessed by fasting C-peptide at baseline and Week 24. The glycemic biomarker (HbA1c) will be further evaluated based on the baseline fasting C-peptide levels and therefore to provide evidence that iGlarLixi is effective regardless of baseline ß-cell function in patients with T2DM suboptimal controlled with OADs. The effect of iGlarLxi in preservation of ß-cell function could also be evaluated via the change in fasting C-peptide from baseline to Week 24" was added. Added citation "(16)".	Fasting C-peptide is widely used to measure ß-cell function.
Section 6.8.1 Background therapy	Added that for the participants who are eligible for randomization and treated with an SU, a glinide, an alpha-GI, or a DPP-4 inhibitor, the treatment will be stopped before or on the randomization day (V2).	Treatment with insulin secretagogues should be stop earlier to V2, if possible, to have the minimum insulin stimulating effect on the day fasting C-peptide sample is collected.
Section 8.1 Efficacy assessments	Title of Section 8.1.1 "HbA1c and FPG measurement" changed to "HbA1c, FPG and fasting C-peptide measurement". The measurement of fasting C-peptide was included.	Fasting C-peptide is added as one of the efficacy measurements.
Section 8.4.2.1 Randomization visit (V2, Week 0, Day 1)	Added that for the randomization visit the participant must return to the investigational site in the morning in fasting status, "i.e., not having any food or drinks (except for water) for at least 8 hours"	The samples for measurement of C-peptide and FPG should be collected at the fasting state.
Section 9.3.2 Analyses of primary endpoint	Added "Baseline fasting C-peptide level by quartiles" in the "Subgroup analyses of the primary estimand".	A prespecify subgroup analysis by baseline fasting C-peptide levels will be conducted to evaluate clinical outcomes with iGlarlixi vs IDegAsp according to baseline ß-cell functionality.
Section 9.3.3.2 Other secondary endpoints	Fasting C-peptide was added in the analysis of "Other secondary endpoints". "… FPG, and 7-point self-monitored plasma glucose (SMPG)…" changed to "…FPG, 7-point self-monitored plasma glucose (SMPG) and fasting C-peptide…."	Analysis of fasting C-peptide endpoint for the assessment of the "other secondary objective".
Section 10.1.3 Informed consent process	Removed text "The ICF contains 2 separate sections… for any reason during the storage period".	Consistency with ICF.
Section 10.2 Appendix 2 Clinical laboratory tests	Fasting C-peptide added to "Other study specific tests" of Table 8.	Fasting C-peptide is added as one of the central laboratory measurements.

Section # and Name	Description of Change	Brief Rationale
Section 10.3.3 Recording and follow-up of AE and/or SAE	Update the assessment of intensity categories. "Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities." was replaced with "Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated." "Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities." was replaced with "Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc." "Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE." was replaced with "Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden."	Protocol template was updated as per Sanofi standards to be aligned with CDISC.
Section 10.5 Appendix 5 Liver And Other Safety: Suggested Actions And Follow-Up Assessments	Remove duplicated text under figure "Increase in ALT". Added cross-reference to "Section 10.3" for guidance on safety reporting.	Correction missed in protocol.
Section 2.3.1 Risk assessment Section 5.2 Exclusion criteria Section 6.1.2 Training for injection devices Section 10.3.2 Definition of SAE	Minor grammatical and editorial revisions.	Editorial changes to clarify or correct protocol inconsistencies.
Section 8.3.7 Hypoglycemia	Added Citation "(17)".	ADA 2021 recommendation for hypoglycemia classification.

Section # and Name	Description of Change	Brief Rationale
Section 10.7 Appendix 7: Abbreviations and throughout the document	Added “IMP: Investigational medicinal product” and “SMPG: Self-monitored plasma glucose”.	Formatting updated throughout as per Sanofi standards.
Section 11 References	Added references 16 (Ferrannini et al 2022) and 17 (American Diabetes Association 2021).	References to support the rationale of adding C-peptide analyses and the hypoglycemia classification, respectively.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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 insufficiently controlled with oral antidiabetic drug(s)

Brief title: iGlarLixi vs IDegAsp in Chinese participants after OAD(s)

Rationale: Premixed insulins are widely used in China (1) either as initial injectable therapy or as insulin treatment advancement. It is therefore meaningful to generate data showing the benefit of iGlarLixi over premixed insulins in different populations of people with T2DM. Fixed-ratio combinations (FRCs) of basal insulin and GLP-1 RAs can provide a novel alternative to premix insulin for therapy advancement. The SoliMix study showed that once daily iGlaLixi, is an efficacious and well-tolerated regimen that is simpler for the participant, providing better glycemic control with less hypoglycemia compared with the twice-daily premix insulin analog Biasp 30 as an alternative for advancing therapy in people with Type 2 diabetes previously suboptimaly controlled with basal insulin plus OADs (2). Given the high use of premix insulin as first injectable therapy in China (3) it is also very important to compare iGlarLixi and premix insulins in Chinese people with T2DM insufficiently controlled with OADs. IDegAsp is arising as preferred option for mixed insulin formulations and as such is considered as key comparator for new data generation.

Thus, the proposed study will be a prospective, randomized, controlled trial to assess the efficacy and safety of iGlarLixi vs IDegAsp in people with T2DM inadequately controlled on metformin with or without a second OAD.

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 HbA1c target, proportion of participants at target without weight gain and/no hypo after 24 weeks of treatment	• 2a Change in HbA1c from baseline to Week 24 • 2b Change in body weight from baseline to Week 24 • 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 and no hypoglycemia (defined as ADA Level 1, 2 or 3)

Objectives	Endpoints
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 eek 24 (each time point and average daily value) • Proportion of participants reaching Hba1c target <7% with no hypoglycemia (defined as ADA level 1, 2 or 3) • Proportions of participants reaching HbA1c target <7% with no clinically relevant hypoglycaemia (defined as ADA level 2 or 3) • 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

Overall design:

- Open-label, 1:1 randomized, active-controlled, 2 treatment-arm, 24-week treatment duration, parallel-group, multicenter Phase 3 study comparing iGlarLixi to IDegAsp.
- The randomization will be stratified by value of screening HbA1c (<8%, ≥8%), and by use at screening of metformin alone or metformin +SGLT2 (Yes/No). Participants with Type 2 diabetes mellitus (T2DM) diagnosed for at least 1 year before the screening visit will be eligible to participate in the study, if they satisfy the inclusion and exclusion criteria.

Brief summary:

This is a parallel-group treatment, Phase 3, randomized, 2-arm study to assess the efficacy and safety of iGlarLixi to IDegAsp in Chinese T2DM participants insufficiently controlled with oral antidiabetic drug(s).

Study details include:

- Study duration per participant: approximately up to 27 weeks
- Treatment duration: 24 weeks

- Visit frequency: after screening (an on-site visit), on-site or phone call visit every 1 week from randomization till Week 4, every 2 weeks till Week 12 and then every 3 weeks till Week 24 (End of Treatment). There will be 14 visits including 7 phone call and 7 on-site visits in total during screening and treatment periods. There will be a safety follow-up by a phone call visit (End of Study) in 3 days after the last dose of the treatment.
- Health measurement/Observation: change in HbA1c as the primary endpoint.
- Intervention name: iGlarLixi and IDegAsp
- Participant sex: male and female
- Participant age range: adults at least 18 years of age
- Condition/disease: Type 2 diabetes mellitus
- Study hypothesis: Compared to IDegAsp, iGlarLixi will demonstrate a similar therapeutic effect on glycemic control assessed by change in HbA1c from baseline to Week 24 in the study participants.

Number of participants:

Approximately 580 participants will be enrolled, and 290 participants will be randomized to each treatment group.

Note: Enrolled participants are all participants from screened participants who have been allocated to an intervention regardless of whether the intervention was received or not.

Intervention groups and duration:

Study intervention(s)

Investigational medicinal product(s)

iGlarLixi

- Formulation: iGlarLixi will be supplied as a sterile aqueous solution in 2 different pen-injectors with 2 different ratios (100 U/mL insulin glargine with 100 or 50 µg/mL lixisenatide depending on the pen-injector). iGlarLixi must not be mixed with other insulins nor diluted.
- Administration device: iGlarLixi will be self-administered with a pen-injector device.

  There will be 2 pen-injectors with different insulin glargine/lixisenatide fixed ratios which allow insulin glargine titration from 5 U/day to 40 U/day while limiting lixisenatide dose to a maximum of 20 µg/day:

  - 1:1 Pen: pen-injector with 3 mL of a sterile aqueous solution of 100 U/mL insulin glargine and 100 µg/mL lixisenatide (1 unit of insulin glargine per 1 µg lixisenatide). This pen-injector is to be used for the iGlarLixi treatment initiation and administration of daily iGlarLixi doses between 5 and 20 dose steps (5 U insulin glargine / 5 µg lixisenatide and 20 U insulin glargine / 20 µg lixisenatide) in increments of 1 dose step.

- 2:1 Pen: pen-injector with 3 mL of a sterile aqueous solution of 100 U/mL insulin glargine and 50 µg/mL lixisenatide (2 units of insulin glargine per 1 µg lixisenatide). This pen-injector is to be used for administration of daily iGlarLixi doses between 21 and 40 dose steps (21 U insulin glargine / 10.5 µg lixisenatide and 40 U insulin glargine / 20 µg lixisenatide) in increments of 1 dose step.

iGlarLixi pen-injectors will be provided to participants randomized to the iGlarLixi group at randomization visit and thereafter.

- Route(s) of administration: subcutaneous (SC) injection
- Dose regimen:

iGlarLixi will be self-administered once daily in the morning in the hour (0 to 60 minutes) before the first meal.

- Starting dose

iGlarLixi is to be initiated with the 1:1 Pen. The starting dose is 5 to 10 dose steps (5 to 10 U insulin glargine/5 to 10 µg lixisenatide) based on investigator's clinical judgment.

- Dose adjustment

After the first week, doses will be titrated once a week according to the dose adjustment algorithm to achieve glycemic target of fasting SMPG ≥80 and ≤100 mg/dL (≥4.4 and ≤5.6 mmol/L) while avoiding hypoglycemia. Thereafter, until the end of the treatment, the dose will be adjusted as necessary to maintain this fasting SMPG target. A total daily dose greater than 40 dose steps (40 U insulin glargine / 20 µg lixisenatide) is not allowed.

IDegAsp (Ryzodeg® 70/30)

- Formulation: IDegAsp will be supplied as a sterile aqueous solution in a Ryzodeg 70/30 FlexTouch. IDegAsp pen must not be mixed with other insulins nor diluted.
- Pen-injector device: IDegAsp will be self-administered with FlexTouch®. The IDegAsp pen contains 3 mL of a sterile aqueous solution of 100 U/mL insulin Degludec and insulin Aspart with a ratio of 70:30.
- Route(s) of administration: subcutaneous (SC) injection
- Dose regimen:

IDegAsp will be self-administered once daily prior to the largest meal of the day according to the locally approved label. The injection time will be determined at the discretion of participants and Investigators on the day of randomization and should remain about the same until the end of the treatment period.

- Starting dose:

The recommended starting daily dose is 5 U -10 U based on Investigator's clinical judgement.

- Dose adjustment:

After the first week, dose will be adjusted weekly following same treat to target principle as for iGlarLixi. The titration algorithm recommended for iGlarLixi can be considered as

reference or titration can follow clinical practice as per investigator´s discretion. Thereafter, until the end of the treatment the dose will be adjusted as necessary to maintain this fasting SMPG target. No dose cap will be set to the upper limit.

Non-investigational medicinal products (NIMP)

Background therapy metformin ± SGLT-2 inhibitor and rescue therapy are considered as non-investigational medicinal products (NIMPs).

Route(s) of administration: Oral administration for metformin and SGLT-2 inhibitor.

Dose regimen: Background treatments metformin ± SGLT-2 inhibitor will be administered orally according to the locally approved label. Metformin will be reimbursed by the Sponsor. A SU, a glinide, an alpha-GI, or a DPP-4 inhibitor, if previously taken, will be stopped at the randomization visit. Metformin is mandatory background therapy. Daily metformin dose will be maintained until the end of the treatment unless there is a specific safety issue related to this treatment. SGLT-2 inhibitors, if previously taken, should be continued at stable dose throughout the treatment period unless there is a specific safety issue related to this treatment.

- Formulation: consistent with local labelling

Posttrial access to study medication: Not applicable

Duration of study intervention:

The total duration of study participation for each participant is up to 27 weeks which includes upto 2 weeks of screening, 24 weeks of treatment period and 3 days of follow up period.

Statistical considerations:

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%

Analysis populations: the efficacy analyses will be performed in the intent-to-treat (ITT) population, comprising all randomized participants. Participants will be analyzed according to the treatment group allocated by randomization. The non-inferiority analysis will also be performed in the per-protocol population, defined as participants from ITT who completed 24 weeks of randomized treatment and have no major or critical protocol deviation that can potentially affect efficacy analysis.

Safety data will be analyzed in the safety population, defined as all randomized participants who take at least 1 dose of study intervention; participants will be analyzed according to the intervention they actually received.

Primary analysis:

The primary estimand of change in HbA1c from baseline to Week 24 will be analyzed under the policy strategy measurements after treatment discontinuation and initiation of rescue medication, regardless of the occurrence of the intercurrent event.

The primary analysis will be based on an ANCOVA model in the ITT population, with missing data imputed by multiple imputations using missingness patterns based on treatment completion, and under the missing at random (MAR) assumption within each pattern.

Within each imputed dataset, the change in HbA1c from baseline to Week 24 will be analyzed using ANCOVA with treatment group and previous OADs as fixed effects, and baseline HbA1c value as continuous 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.

Analysis of secondary endpoints:

Continuous secondary endpoints will be analyzed using the similar ANCOVA model as the primary endpoint, adjusting for treatment groups, randomization strata and appropriate baseline covariates. Categorical endpoints will be analyzed using logistic regression model adjusting for treatment groups, randomization strata and appropriate baseline covariates. Summaries will be prepared for safety and tolerability findings.

Multiplicity adjustment: to control overall type 1 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.

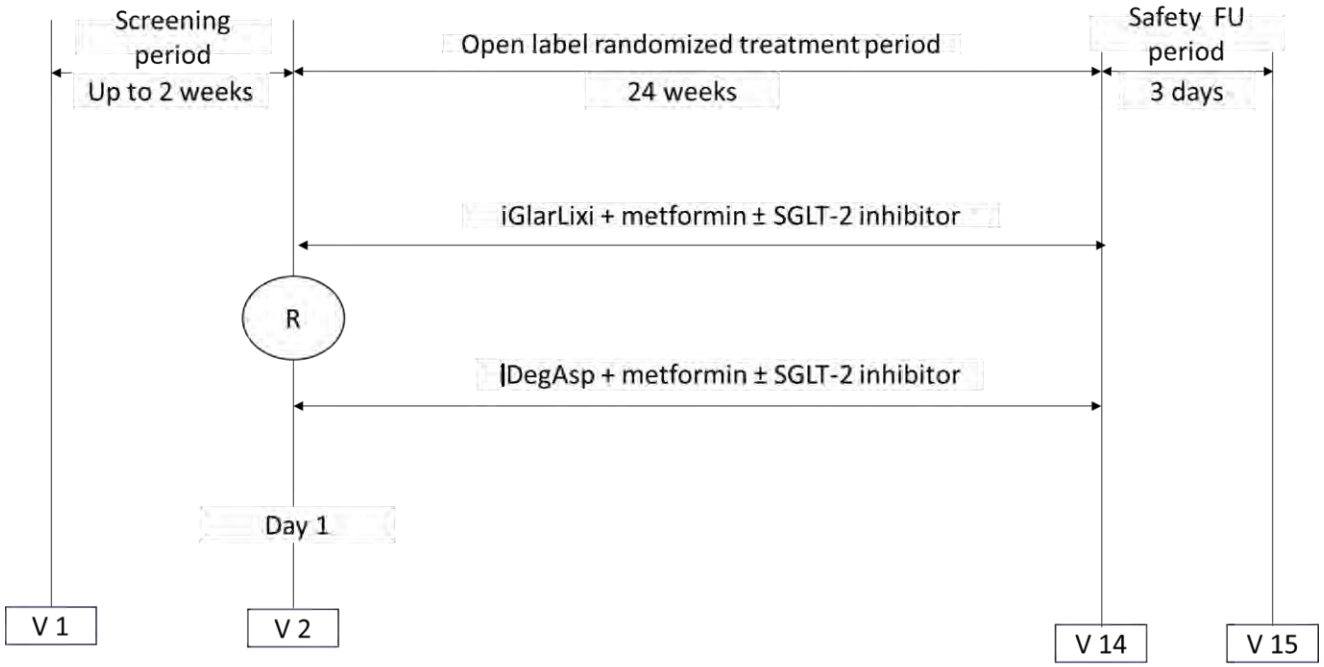
If the primary endpoint is statistically significant at the 2-sided 0.05 level, a hierarchical testing procedure will be performed to test the key secondary efficacy endpoints.

For other secondary hypotheses, no multiplicity adjustment will be applied.

Data Monitoring/Other committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



1.3 SCHEDULE OF ACTIVITIES (SOA)

Study period	Screening	Randomization	Study treatment period													Follow-up
Visit number	1	2[a]	3	4	5	6	7	8	9	10	11	12	13	14	E/D[d]	15
Visit type (on-site/phone)[b]	site	site	☎	site	☎	site	☎	site	☎	site	☎	site	☎	site	site	☎
Week[b]	-2	0 (Day 1)	1	2	3	4	6	8	10	12	15	18	21	24	E/D	24 + 3 days
Window (days)[c]			±2	±2	±2	±2	±3	±3	±3	±3	±4	±4	±4	±4		-1/+3
Informed Consent	X															
Inclusion/Exclusion criteria	X	X														
Demography	X															
Medical, surgical, diabetes history, alcohol & smoking habits, prior medications	X															
Physical Examination	X	X								X				X	X	
Height	X															
Body weight	X	X		X		X		X		X		X		X	X	
Vital Signs[e]	X	X		X		X		X		X		X		X	X	
12-lead ECG	X													X	X	
Diet and Lifestyle counseling		X														
IRT contact	X	X		X		X		X		X		X		X	X	X
Concomitant medication recording																
AE/SAE/Hypoglycemia[f]																
Glucometer dispensation & training (including training on glucose measurements)[g]	X															
Diary dispensation / collection (reviewed at each on-site visit)	X	X		X		X		X		X		X		X	X	
Pen-injector and self-injection training[g]		X														
Fasting SMPG[h]		X	X	X	X	X	X	X	X	X	X	X	X	X		
7-point SMPG profiles (on 2 days in the week prior to the visit)[i]		X								X				X		
IMPs dispensation		X		X		X		X		X		X				
Record of IMPs doses[j]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Count returned pen-injectors				X		X		X		X		X		X	X	
Dose titration compliance check			X	X	X	X	X	X	X	X	X	X	X	X	X	
Central Laboratory tests																
HbA1C	X					X		X		X		X		X	X	

Study period	Screening	Randomization	Study treatment period													Follow-up
Visit number	1	2[a]	3	4	5	6	7	8	9	10	11	12	13	14	E/D[d]	15
Visit type (on-site/phone)[b]	site	site	☎	site	☎	site	☎	site	☎	site	☎	site	☎	site	site	☎
Week[b]	-2	0 (Day 1)	1	2	3	4	6	8	10	12	15	18	21	24	E/D	24 + 3 days
FPG[m]	X	X				X		X		X		X		X	X	
Fasting C-peptide[m]		X												X[n]	X	
Safety laboratory[k] hematology, serum chemistry	X					X		X		X		X		X	X	
Amylase, lipase,	X					X		X		X		X		X	X	
calcitonin	X															
FSH, estradiol (if necessary to confirm menopausal status)	X															
Urine pregnancy test[l] (women childbearing potential only)	X	X		X		X		X		X		X				

a Randomization (V2) can be performed less than 2 weeks after screening visit (V1) if the laboratory data are available.

b Additional phone calls between visits for titration purposes should be scheduled as often as deemed necessary by the Investigator

c Visit widows listed in the table are acceptable always using Day 1 (V2) as reference. A visit window of -1 day or +3 days for the post-treatment follow-up visit (V15) is acceptable using the day of V14 as reference. If one visit date is changed, the next visit should take place according to the original schedule.

d **E/D= Early IMP discontinuation**, participants should have an onsite visit as soon as possible with the assessments (except 7-point SMPG) normally planned at the end of treatment visit (V14). Afterward, the patients should continue in the study up to the scheduled date of study completion. They should be followed up according to the study procedures as specified in the protocol. **In case of rescue therapy**, all assessments (except 7-point SMPG) planned at V14 should be performed before starting rescue therapy, participants then continue the study treatment (including background therapy if appropriate), and all visits and assessments should be performed as scheduled.

e Systolic and diastolic blood pressure, heart rate.

f Whenever the participant feels hypoglycemic symptoms, plasma glucose should be measured by the participant (or others, if applicable), if possible. Participants 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.

g Glucose meter and training will be provided to all participants. For the participants that will return to visit 2, sites should make a reminder phone call to remind participants about the 7-point SMPG performance on 2 days in the week prior to Visit 2. Pen injection training will be provided at Visit 2 and additional training is needed if patients need to switch injection pen from 1:1 Pen to 2:1 Pen (iGlarLixi).

h Fasting SMPG should be measured by the participant before the first meal and before the administration of the glucose-lowering agents (IMP or background therapy if appropriate) once a day from Day 1 (V2) to Week 12 (V10) and then at least 3 days per week till the end of treatment (Week 24) (see Section 8.1.3.1 or daily fasting SMPG values to be entered in the eCRF).

i The 7-point SMPG profile should be measured at the following 7 points: preprandial and 2 hours postprandial for breakfast, lunch, dinner and at bedtime in any two days in the week prior to the visit. Participants should be reminded to perform the 7-point SMPG profile or, the onsite visit should be postponed allowing for the performances.

j The following IMP dose info (iGlarLixi and IDegAsp) will be entered in the eCRF: prior to V10 (Week 12): all available data of IMP doses, injection time and type of pen (iGlarLixi only), including missed IMP injections; after V10 (Week 12): if the dose is not adjusted, the IMP dose and injection time on the last 3 days in the week before each visit. IMP doses and injection time will be recorded in case of dose modification, missed dose and on the 7-point SMPG performing days. Dose and injection time in case of confirmed hypoglycemia (if appropriate); all available data of IMP doses and injection time on the last 3 days before permanent IMP treatment discontinuation or rescue therapy.

k Safety Laboratory: hematology = WBC, RBC, hemoglobin, hematocrit, platelets, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils). Serum chemistry = total bilirubin, G-GT, AST, ALT, ALP, creatinine, eGFR, uric acid, sodium, potassium, phosphorus, calcium.

l Urine pregnancy test in female of childbearing potential only will be performed at study sites (local).

m Participants must be in fasting status, not have any food and drinks (except for water) for at least 8 hours.

n Fasting C-peptide sample at Visit 14/Week 24 should be only collected for participants who have C-peptide samples collected at Visit 2/Week0.

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; D = day; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; FSH = follicle stimulating hormone; G-GT = gamma-glutamyl transpeptidase; HbA1c = glycated hemoglobin A1c;; IMP = investigational medicinal product; IRT = interactive response technology; RBC = red blood cell; SAE= serious adverse event; SMPG = self-monitored plasma glucose; V = Visit; WBC = white blood cell.

2 INTRODUCTION

iGlarLixi is a fixed-ratio combination of insulin glargine 100 u/mL (Lantus®) and the GLP-1 RA lixisenatide that is developed for treatment of T2DM.

2.1 STUDY RATIONALE

Premixed insulins are widely used in China (1) either as initial injectable therapy or as insulin treatment advancement. It is therefore meaningful to generate data showing the benefit of iGlarLixi over premixed insulins in different populations of people with T2DM. Fixed-ratio combinations (FRCs) of basal insulin and GLP-1 RAs can provide a novel alternative to premix insulin for therapy advancement. The SoliMix study showed that once daily iGlarLixi, is an efficacious and well-tolerated regimen that is simpler for the participant, providing better glycemic control with less hypoglycemia compared with the twice-daily premix insulin analog Biasp 30 as an alternative for advancing therapy in people with type 2 diabetes previously suboptimally controlled with basal insulin plus OADs (2). Given the high use of premix insulins as first injectable therapy in China (3) it is also very important to compare iGlarLixi and premix insulins in Chinese people with T2DM insufficiently controlled with OADs. IDegAsp is arising as preferred option for mixed insulin formulations and as such is considered as key comparator for new data generation.

Thus, the proposed study will be a prospective, randomized, controlled trial conducted in China to assess the efficacy and safety of iGlarLixi vs IDegAsp in people with T2DM inadequately controlled on metformin with or without a second OAD.

2.2 BACKGROUND

Despite novel therapeutic options, many people with type 2 diabetes (T2D) do not achieve their individualized HbA1c targets. Close to 50% of participants with type 2 diabetes treated in routine practice using any type of therapy do not maintain an A1C value <7.0%, and ~22% have an A1C value >8.0% (3).

Given the progressive nature of T2D, many individuals un-controlled with multiple oral agents will require advancement to injectable therapy using either a glucagon-like peptide-1 receptor agonist (GLP-1 RA), recently recommended as a first option, or traditionally a basal insulin (4).

Premix insulins remain frequently used in several countries including China, either as initial injectable therapy or as insulin treatment advancement (1). Premix insulin injections can potentially provide significant glycemic improvements but at the expense of increased hypoglycemia and weight gain, which may affect treatment adherence (5). Real-world evidence suggests that glycemic control often remains suboptimal with premix insulins (5).

Fixed-ratio combinations (FRCs) of basal insulin and GLP-1 RAs can provide a novel alternative to premix insulin for therapy advancement. iGlarLixi combines two different glucose-lowering agents with complementary mechanisms of action. Insulin glargine is a long-acting basal insulin

that targets mainly FPG levels by mimicking physiologic insulin secretion to provide peakless insulin levels over a 24-hour period. Lixisenatide is a once-daily GLP-1 receptor agonist that increases insulin levels and decreases glucagon secretion in a glucose-dependent manner, minimizing the risk of treatment-related hypoglycemia. Lixisenatide also slows gastric emptying, thereby diminishing PPG excursions (6). The development of the fixed-ratio combination of insulin glargine and lixisenatide follows a participant-centric treatment approach. With iGlarLixi, reaching HbA1c targets is a result of both titration of insulin glargine to fasting glucose targets and a concomitant increase of the lixisenatide dose with a corresponding improvement in PPG control.

Efficacy and Safety of iGlarLixi compared to basal insulin and GLP-1RA have been comprehensively assessed in global trials Lixilan-O, LixiLan-L and LixiLan-G (7, 8, 9). Similar trials have also been conducted in Japanese participants (10, 11, 12). All these studies have shown that iGlarLixi has superior efficacy in HbA1c reduction compared to basal insulin and GLP-1RAs, with no additional hypoglycemic risk and significantly less weight gain compared to basal insulin, and less gastrointestinal side effects compared to GLP-1RAs.

In China, phase III studies of iGlarLixi were recently conducted in T2DM participants inadequately controlled with OAD(s) and in participants inadequately controlled with basal insulin ± OADs. Data is expected to be released by end of 2021 -2022.

IGlarlixi is approved in around 70 countries, among them in the United States (2016), Europe (2017) and Japan (2020). Approval in China is expected by 2022 (13, 14, 15).

The simplified treatment regimen, high efficacy with weight neutrality and the absence of increased risk of hypoglycemia shown with iGlarLixi are likely to have positive impacts on treatment adherence.

Fixed-ratio combinations (FRCs) of basal insulin and GLP-1 RAs can provide a novel alternative to premix insulin for therapy advancement. It is therefore meaningful to generate data showing the benefit of iGlarLixi over premixed insulins in different populations of people with T2DM. The SoliMix study showed that once daily iGlaLixi, is an efficacious and well-tolerated regimen that is simpler for the participant, providing better glycemic control with less hypoglycemia compared with the twice-daily premix insulin analog Biasp 30 as an alternative for advancing therapy in people with type 2 diabetes previously sub optimally controlled with basal insulin plus OADs (2).

Up to date there is no direct data comparing a FRC to a premix insulin formulation in participants sub optimally controlled on OADs.

Premix insulins are widely used as first injectable therapy in China. Thus, the proposed study will be a prospective, randomized, controlled trial conducted in China to assess the efficacy and safety of iGlarLixi vs IDegAsp in people with T2DM inadequately controlled on metformin with or without a second OAD.

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Risk assessment

Table 1 - Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention:		
Hypersensitivity to any of its ingredient Hypoglycemia caused by the study interventions Overdose due to medication errors Injection site reactions GI AEs, including nausea, diarrhea, and vomiting caused by iGlarLixi (lixisenatide) Acute pancreatitis Thyroid medullary cell cancer	For details about data and rational of the risks, please refer to the current version of Investigator's Brochure, Section 7.	Participants with known allergy to GLP-1 RA or insulin products will be excluded. investigator will educate the participants to seek immediate medical attention if suspected event with symptoms and signs. Participants will be monitored for hypoglycaemia through SMPG and to be educated how to treat hypoglycemia at home or seek to medical attention as needed. Participants will be well trained in self -injection before the 1st dosing and at the time when a participant needs to shift injection pen from 1:1 to 2:1 pen (iGlarLixi). In addition, there will be more training opportunities in case any injection issue is observed at the onsite visits. The occurrence of dosing error could be efficiently minimized. Participants will be educated to change injection location (abdominal wall, thighs or upper arms) at each time of injection to avoid the injection site skin reaction. The GLP-1 class effect of GI reactions will be reduced with low starting dose (5 µg/lixisenatide). With the titration procedure ie, dose increase every week, the participants may tolerate better to higher doses (up to 20 µg). Patients with amylase and/or lipase >3 times the upper limit of normal (ULN) will be excluded from participation in this study. Pancreatic enzymes will be monitored during the study. Participants are instructed to seek medical attention and report any symptoms of abdominal pain to the investigator. C-cell hormone calcitonin is measured at screening and patients with calcitonin ≥20 pg/mL (5.9 pmol/L) will be excluded from participation in the study.
Study procedures: Not applicable		
Other: Not applicable		

2.3.2 Benefit assessment

- Potential benefit of receiving study intervention known to improve glycemic control during the study duration
- Contributing to the process of developing new therapies in an area of treatment of T2DM
- Medical evaluations/assessments associated with study procedures [eg, physical exam, ECG, glycemic assessments etc].

2.3.3 Overall benefit: risk conclusion

The investigational medicinal products (IMPs) administered in this study (iGlarLixi and IDegAsp) have demonstrated glucose lowering properties and are both approved for the treatment of adult participants with T2DM. iGlarLixi has been approved in more than 70 countries worldwide including the United States, the European Union, and Japan and is under review in several other countries (including China). Given the safety profile observed during development and confirmed by post-marketing data, iGlarLixi is considered to be well tolerated and reflective of the individual components, with no new risk identified for the population to be included in this study. In addition, treatment with both iGlarLixi and premixed IDegAsp is in line with current approved label indications. Therefore, the risk for participants participating in this study, using daily doses of iGlarLixi up to 40 U of insulin glargine/20 µg of lixisenatide is considered acceptable. All participants entering this study will receive treatment with iGlarLixi or IDegAsp on top of metformin or metformin + SGLT2i. In addition, all participants will benefit from close management of their T2DM. Rescue therapy is planned and described in the clinical study protocol for participants whose glycemia remains poorly controlled. Given the expected improvement of metabolic control and the additional measures to improve diabetes management, these benefits are considered to outweigh the potential risk associated with the iGlarLixi and premixed insulin. Therefore, the benefit-risk ratio for participants participating in this study is considered favorable.

3 OBJECTIVES AND ENDPOINTS

Table 2 - 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
Secondary efficacy	
• 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	• 2a Change in HbA1c from baseline to Week 24 • 2b Change in body weight from baseline to Week 24 • 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 and no hypoglycemia (defined as ADA level 1,2 or 3)
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% with no hypoglycemia (defined as ADA level 1, 2 or 3) • Proportions of participants reaching HbA1c target <7% with no clinically relevant hypoglycemia (defined as ADA level 2 or 3) • 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 1-2-3) • AEs, SAEs, AESIs, and AEs leading to treatment discontinuation, vital signs and safety laboratory values

3.1 APPROPRIATENESS OF MEASUREMENTS

The primary efficacy variable is HbA1c values which reflects the glycemic history of the previous 120 days and is thus an index of mean glycemia, documenting glycemic control over the past 2 to

3 months. HbA1c has also been shown to correlate with the development of long-term complications of diabetes, and reduction of HbA1c is known to reduce the risk of long-term microvascular complications. Therefore, HbA1c is considered an appropriate primary endpoint for assessing the effect of a treatment on glycemic control. In addition to the analysis of the change from baseline in HbA1c, the responder analysis allows the clinical relevance of the reduction observed in HbA1c to be demonstrated. The duration of study treatment is considered to be sufficient for achieving stable conditions with IMP after dose titration and for enabling an adequate assessment of time dependent changes in HbA1c and the concomitant risk of hypoglycemia.

The problem of weight gain in T2DM is widely recognized. Consequently, iatrogenic weight gain is not only unwelcome, but represents an important clinical issue that can become a barrier to the successful management of glycemic control. Body weight control is one of the reasons to choose a GLP-1 RA instead of rapid-acting insulin to intensify basal insulin therapy in this overweight or obese type 2 diabetes population. Taking into account the major impact of insulin-related body weight gain, it is appropriate to include body weight change as secondary efficacy endpoint.

Insulins target primarily, although not exclusively, fasting hyperglycemia, therefore, assessment of fasting glucose is relevant in this study. The 7-point SMPG profiles are also considered as a valuable parameter for monitoring the overall glycemic control throughout the day. ß-cell function will be assessed by fasting C-peptide at baseline and Week 24. The glycemic biomarker (HbA1c) will be further evaluated based on the baseline fasting C-peptide levels and therefore to provide evidence that iGlarLixi is effective regardless of baseline ß-cell function in patients with T2DM suboptimal controlled with OADs. The effect of iGlarLxi in preservation of ß-cell function could also be evaluated via the change in fasting C-peptide from baseline to Week 24 (16).

Composite outcomes such as decrease in HbA1c not associated with body weight gain and/or with hypoglycemia events are also of interest in the management of T2DM and will be investigated in this study. Along with HbA1c, other glycemic measures such as FPG and SMPG would be assessed as secondary endpoints in this study.

The duration of study treatment is considered to be sufficient for achieving stable conditions with IMP and for enabling an adequate assessment of time-dependent changes in HbA1c and the concomitant risk of hypoglycemia.

Safety will be evaluated by standard clinical measurements. The study interventions administered in this study are approved with well-established safety profiles; additionally, routine post-baseline laboratory testing will be performed. Specific safety parameters of interest for a glucose lowering agent such as hypoglycemia and known GLP-1 AR class side effect of GI AEs will also be assessed.

4 STUDY DESIGN

4.1 OVERALL 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 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 +SGLT2 (Yes/No). 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

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

- IDegAsp 70/30 (Ryzodeg) is arising as one of the preferred options as co-formulation of basal and prandial insulin and so generating this data vs IDegAsp is of clinical relevance.
- Randomized, controlled study design is widely considered the best and most rigorous way of investigating interventional medicine
- Given the high use of premixed insulins as initial injectable therapy in China, it is of special interest to compare iGlarLixi and IDegAsp in Chinese people with T2DM insufficiently controlled with OADs
- Improvement in HbA1c is a standard surrogate outcome measure recognized by the medical community and Health Authorities as an appropriate primary endpoint for assessing the effect of anti-diabetic treatments on glycemic control.

4.3 JUSTIFICATION FOR DOSE

Study intervention is discussed in Section 6 with details of starting dose and dose justification during the treatment period.

4.4 DURATION OF STUDY PARTICIPATION

4.4.1 Duration of study participation for each participant

The maximum study duration per participant will be approximately 27 weeks (comprised of a screening period of up to 2 weeks, a 24-week open-label randomized treatment period, and a 3-day post-treatment safety follow-up period).

4.4.2 Determination of end of clinical trial (all participants)

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

The sponsor can terminate the Trial prematurely based on any unforeseen developments.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be at least 18 of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants who are diagnosed with T2DM for at least 1 year before the screening visit

I 03. Participants who are treated for at least 3 months prior to the screening visit with a stable dose of metformin (at least 1000 mg/day or the maximum tolerated dose) alone or in combination with a second oral antidiabetic treatment that can be a sulfonylurea (SU), a glinide, an alpha-glucosidase inhibitor (alpha-GI), a dipeptidyl-peptidase-4 (DPP-4) inhibitor or a sodium-glucose co-transporter 2 (SGLT-2) inhibitor

I 04. HbA1c at screening visit:

- between 7.5% and 11%, both inclusive, for participants previously treated with metformin alone or + SGLT-2 inhibitor, or
- between 7.0% and 10%, both inclusive, for participants previously treated with metformin + a second oral antidiabetic treatment other than SGLT-2 inhibitor.

I 05. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.

Weight

I 06. Body mass index (BMI) <40 kg/m² at screening

Sex, contraceptive/barrier method and pregnancy testing requirements

I 07. Male or female, including females of childbearing potential who agree to use contraception during the study duration

Informed Consent

I 08. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Participant who has a severe renal function impairment with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2

E 02. Pregnant or breast-feeding woman.

E 03. Woman of childbearing potential not protected by highly effective contraceptive method of birth control and/or who is unwilling or unable to be tested for pregnancy

E 04. Conditions/situations such as:

- Participant with short life expectancy.
- Participant with conditions/concomitant diseases making him/her not evaluable for the primary efficacy endpoint (eg, hemoglobinopathy or hemolytic anemia, receipt of blood or plasma products within 3 months prior to screening).
- Participant with conditions/concomitant diseases precluding his/her safe participation in this study (eg, active malignant tumor, major systemic diseases, presence of clinically significant diabetic retinopathy or presence of macular edema likely to require laser treatment within the study period).
- Uncooperative or any condition that could make the participant potentially non-compliant to the study procedures (eg, participant unable or unwilling to do self-injections or blood glucose monitoring using the Sponsor-provided blood glucometer at home).

Prior/concomitant therapy

E 05. 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.

E 06. Use of oral or injectable glucose-lowering agents other than those stated in the inclusion criteria within 3 months prior to screening.

E 07. Use of systemic glucocorticoids (excluding topical application or inhaled forms) for 1 week or more within 3 months prior to screening.

E 08. Use of weight loss drugs within 3 months prior to screening.

E 09. History of discontinuation of a previous treatment with GLP-1 RAs due to safety/tolerability reasons or lack of efficacy.

E 10. Use of any investigational drug other than specified in this protocol within 1 month or 5 half-lives, whichever is longer, prior to screening.

Other exclusions

E 11. Laboratory findings tested at the screening visit:

- Amylase and/or lipase >3 times the upper limit of normal (ULN) laboratory range.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 ULN.

- Total bilirubin >1.5 ULN (except in case of Gilbert's syndrome).
- Calcitonin ≥20 pg/mL (5.9 pmol/L).
- Hemoglobin <10.5 g/dL and/or neutrophils <1500/mm^3 and/or platelets <100 000/mm^3.
- Positive urine pregnancy test in female of childbearing potential.

E 12. Contraindication to metformin and/or SGLT-2 inhibitor use, for those who were taking it prior to the study, according to local labeling, warning/precaution of use (when appropriate) as displayed in the respective National regulation

E 13. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized

E 14. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures

E 15. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with section 1.61 of the ICH-GCP Ordinance E6)

E 16. Any specific situation during study implementation/course that may raise ethics considerations

E 17. Sensitivity to any of the study interventions (insulin or, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study

E 18. Participants who withdraw consent at randomization or are loss to follow up at randomization visit.

5.3 LIFESTYLE CONSIDERATIONS

Lifestyle and diet therapy provided before the time of screening is to be continued during the study. Dietary and lifestyle counseling will be given by a healthcare professional on the day of randomization and as needed during the study, which should be consistent with international or local guidelines for participants with T2DM (with regard to the distribution of calories among carbohydrates, proteins, and fats, exercise, etc.).

Compliance with the diet and lifestyle counseling will be assessed in case of insufficient glucose control.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of

Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

A participant should not be randomized more than once. In cases where original screen failure was due to reasons expected to change during rescreening and based upon the Investigator's clinical judgment, the participant can be rescreened one time for this study.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 6 (Section 10.6: Contingency measures for a regional or national emergency that is declared by a governmental agency) should be considered for screening/enrollment/randomization/administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 3 - Overview of study interventions administered

Intervention label	Intervention label 1	Intervention label 2	Non-Interventional
Intervention name	iGlarLixi	IDegAsp	Metformin ± SGLT-2 inhibitor
Type	Drug	Drug	Drug
Dose formulation	Pen injector	Pen injector	Tablet
Unit dose strength(s)	2 types of SoloStar pens with 2 different ratios of 1:1 or 2:1 (100 U/mL insulin glargine with 100 or 50 µg/mL lixisenatide). Each pen injector contains 3 ml of iGlarLixi solution.	Ryzodeg 70/30 FlexTouch® which contains 3 ml of 100 U/ml of insulin Degludec and insulin Aspart with a ratio of 70:30.	
Dosage level(s)	Dosing time: Once daily in the hour (0 to 60 minutes) before the first meal. Starting dose: Initiated with the 1:1 Pen at a dose of 5-10 dose steps (5-10 U insulin glargine / 5 -10 µg lixisenatide) per Investigator's judgment. Dose modification: Once a week titration according to the algorithm described in Section 6.1.4	Dosing time: Once daily before the largest meal. Time determined at the discretion of participants and Investigators at randomization and to remain unchanged during the treatment Starting dose: 5-10 U per Investigator's judgment. Dose modification: Once a week titration according to investigator´s discretion, or refer to the algorithm described in Section 6.1.4	Metformin ± SGLT-2 inhibitor will be administered orally according to the locally approved label. Daily dose of metformin ± SGLT2 inhibitor (if previously taken) will be continued and maintained at the stable dose until the end of the treatment unless there is a specific safety issue related to this treatment. An SU, a glinide, an alpha-GI, or a DPP-4 inhibitor, if previously taken, will be stopped prior to randomization.
Route of administration	Self- administration via SC injection	Self-administration via SC injection	Oral administration
Use	Experimental	Active comparator	Background intervention
IMP or NIMP	IMP	IMP	NIMP

Packaging and labeling	Study Intervention will be provided in kit. Each kit will be labeled as required per country requirement.	Study Intervention will be provided in kit. Each kit will be labeled as required per country requirement.

Table 4 - Arms and associated interventions

Arm name	1	2
Associated interventions (intervention label[s])	iGlarLixi	IDegAsp

6.1.1 Devices:

Injectors:

iGlarLixi will be self-administered with a pen-injector.

There will be 2 pen-injectors with different insulin glargine/lixisenatide fixed ratios which allow insulin glargine titration from 5 U/day to 40 U/day while limiting lixisenatide dose to a maximum of 20 µg/day:

- 1:1 Pen: pen-injector with 3 mL of a sterile aqueous solution of 100 U/mL insulin glargine and 100 µg/mL lixisenatide (1 unit of insulin glargine per 1 µg lixisenatide). This pen-injector is to be used for the iGlarLixi treatment initiation and administration of daily iGlarLixi doses between 5 and 20 dose steps (5 U insulin glargine / 5 µg lixisenatide- 20 U insulin glargine / 20 µg lixisenatide) in increments of 1 dose step
- 2:1 Pen: pen-injector with 3 mL of a sterile aqueous solution of 100 U/mL insulin glargine and 50 µg/mL lixisenatide (2 units of insulin glargine per 1 µg lixisenatide). This pen-injector is to be used for administration of daily iGlarLixi doses between 21 and 40 dose steps (21 U insulin glargine / 10.5 µg lixisenatide and 40 U insulin glargine / 20 µg lixisenatide) in increments of 1 dose steps.

iGlarLixi pen-injectors will be provided to participants randomized to the iGlarLixi group at randomization visit and thereafter.

IDegAsp (Insulin Degludec and Insulin Aspart Injection) will be supplied as a sterile aqueous solution in a Ryzodeg 70/30 FlexTouch. IDegAsp pen must not be mixed with other insulins nor diluted.

The IDegAsp pen contains 3 mL of a sterile aqueous solution of 100 U/mL insulin Degludec and insulin Aspart with a ratio of 70:30.

All device deficiencies (including malfunction, use error and inadequate labelling) shall be detected, documented, and reported by the Investigator throughout the clinical investigation (see Section 8.3.8) and appropriately managed by the Sponsor.

6.1.2 Training for injection devices

Handling procedures of the pen-injectors administration technique will be provided in specific instructional pen-injectors leaflets. The participants will be trained on how to use the relevant pen injectors and needles correctly, how to store it, and how to change the needle by the study staff and provided with an instruction leaflet at randomization visit (V2, Day 1), for the pen-injector devices listed below.

At V2, depending on the randomized treatment group, participants will be trained on:

- 1:1 pen injector and 2:1 pen injector for participants randomized to receive iGlarLixi
- Ryzodeg 70/30 FlexTouch® for participants randomized to receive IDegAsp

Training will be repeated as often as deemed necessary by study site staff during the treatment period. Additional training is needed if participants need to switch from 1:1 Pen to 2:1 Pen. The pen-injectors and leaflet that the participant will need to use during the treatment period will be dispensed according to the visit. Each participant is supplied with the appropriate number of pen-injectors according to the dispensing scheme indicated in the study flowchart.

Pen-injectors should never be shared with others, even if the needle is changed. Participants must always use a new needle for each injection to help ensure sterility and prevent blocked needles.

Reuse or share needles with another person is not allowed. Participants must remove needles from pen-injectors after each injection completion.

Pen device-related issues (malfunctions) must be reported to the Sponsor via the procedure for product technical complaint (PTC), using the respective PTC form, which is described in a separate manual. See Section 8.3.8 for guidelines for reporting PTC."

6.1.3 Dosage schedule

Injection time

iGlarLixi

iGlarLixi will be self-administered once daily in the morning in the hour (0 to 60 minutes) before the first meal using the pen-injector.

IDegAsp:

IDegAsp will be self-administered once daily before the largest meal of the day using Ryzodeg 70/30 FlexTouch® pen. The injection time will be determined at the discretion of participants and Investigators on the day of randomization and should remain about the same until the end of the treatment period.

Injection site

The study intervention should be administered by deep SC injection, alternating between the left and right anterolateral and left and right posterolateral abdominal wall or thighs or upper arms. Within a given area, location should be changed (rotated) at each time to prevent injection site skin reactions.

6.1.4 Starting dose and dose modification

6.1.4.1 iGlarLixi

Starting dose:

iGlarLixi is to be initiated with the 1:1 Pen. The recommended starting daily dose is 5 dose steps (5 U insulin glargine / 5 µg lixisenatide). A higher starting daily dose up to 10 dose steps (10 U insulin glargine / 10 µg lixisenatide) may be allowed in some cases according to the investigator's clinical judgment that a higher starting dose of iGlarLixi is considered necessary.

A starting daily dose greater than 10 dose steps (10 U insulin glargine / 10 µg lixisenatide) is not allowed, in order not to exceed the recommended starting dose of lixisenatide which is 10 µg.

Dose adjustment:

- After the first week, doses will be titrated once a week according to the dose adjustment algorithm described in Table 5 to achieve glycemic target of fasting SMPG ≥80 and ≤100 mg/dL (≥4.4 and ≤5.6 mmol/L) while avoiding hypoglycemia.
- Thereafter, until the end of the treatment period, the dose will be adjusted as necessary to maintain this fasting SMPG target. A total daily dose greater than 40 dose steps (40 U insulin glargine / 20 µg lixisenatide) is not allowed. Doses may be modified at any time for hypoglycemia.

Dose modification will be based on a median of fasting SMPG values from the last 3 measurements, which may include the value measured on the day of titration, measured by the participant using glucometers and accessories supplied by the Sponsor for this study.

Table 5 - Dose adjustment algorithm for iGlarLixi

Median of fasting SMPG values from the last 3 measurements, which may include the value measured on the day of titration	iGlarLixi dose adjustments (dose step/day)
>140 mg/dL (>7.8 mmol/L)	+ 4
>100 and ≤140 mg/dL (>5.6 and ≤7.8 mmol/L)	+ 2
Glycemic target: ≥80 and ≤100 mg/dL (≥4.4 and ≤5.6 mmol/L)	No change
≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)	- 2
<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) documented in the preceding week	- 2 to -4 or at the discretion of the Investigator or medically qualified designee

Median refers to intermediate SMPG value (the value between the lowest and the highest SMPG values when the values are ranked in a growing order).

Note: Choice of pen-injector for iGlarLixi:

- If the participant needs a total daily iGlarLixi dose of 5 to 20 dose steps, use the 1:1 Pen (100 U/mL insulin glargine with 100 µg/mL lixisenatide).

- If the participant needs a total daily iGlarLixi dose of 21 to 40 dose steps, use the 2:1 Pen (100 U/mL insulin glargine with 50 µg/mL lixisenatide).

Daily doses of iGlarLixi higher than 40 dose steps (40 U insulin glargine / 20 µg lixisenatide) must not be administered. In case a dose >40 dose steps iGlarLixi is needed to maintain HbA1c below predefined threshold value for rescue, the dose must be kept at 40 dose steps and a rescue therapy should be introduced (see Section 6.8.4 for rescue therapy).

6.1.4.2 IDegAsp:

Starting dose:

The recommended starting daily dose is 5 U. A higher starting daily dose up to 10 U may be allowed in some cases if according to clinical judgment the investigator believes that a higher starting dose might be necessary. A starting daily dose greater than 10 U is not allowed.

Dose modification:

After the first week, dose will be adjusted weekly to reach and maintain glycemic target of fasting SMPG ≥80 and ≤100 mg/dL (≥4.4 and ≤5.6 mmol/L) while avoiding hypoglycemia. Titration should be based on median of fasting SMPG of 3 consecutive days measurements. According to their best clinical judgement, investigators can either follow the algorithm they usually use in their daily medical practice or the recommended algorithm below which is similar as used for iGlarlixi

Table 6 - Dose adjustment algorithm for IDegAsp

Median of fasting SMPG values from the last 3 measurements, which may include the value measured on the day of titration	IDegAsp dose adjustments (U/day)
>140 mg/dL (>7.8 mmol/L)	+ 4
>100 and ≤140 mg/dL (>5.6 and ≤7.8 mmol/L)	+ 2
Glycemic target: ≥80 and ≤100 mg/dL (≥4.4 and ≤5.6 mmol/L)	No change
≥60 and <80 mg/dL (≥3.3 and <4.4 mmol/L)	- 2
<60 mg/dL (<3.3 mmol/L) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) documented in the preceding week	- 2 to -4 or at the discretion of the Investigator or medically qualified designee

Median refers to intermediate SMPG value (the value between the lowest and the highest SMPG values when the values are ranked in a growing order).

- **Attention for dose modification (iGlarLixi and IDegAsp):** iGlarLixi or IDegAsp dose titration may be withheld for a week or reduced in a participant who experiences two or more episodes of level 1 and/or level 2 hypoglycemia or one episode of level 3 hypoglycemia (requiring assistance from others to treat the hypoglycemic event)
- Participants who experienced hypoglycemia as a result of a missed meal, unusual exercise, or alcohol use will be counseled on the correction of those behaviors and may not need to have their insulin dose decreased.

- Investigators are allowed to modulate or stop titration or temporarily reduce dosage if they believe further titration would be hazardous to the participant (eg, due to age, comorbid conditions, individual participant considerations, other than hypoglycemia). In such a case the reason for the exceptions should be recorded in the source document.

Good clinical judgment is to be exercised in dose titration for investigators to identify any barriers for participants' titration compliance, eg., diet and exercise, alcohol consumption, and any concomitant illness. Participants should be familiarized with the titration schedule so that they would be able to monitor the titration with the assistance of the investigator or medically qualified designee. Investigators and qualified designees are encouraged to communicate with participants during the dose titration. More frequent contact via telecommunications eg, phone call, text message, WeChat etc can be added between visits if needed.

6.2 STUDY INTERVENTION PACKAGING AND LABELING

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

The appropriate number of kits will be dispensed to cover up to the next dispensing visit (see the study flowchart in Section 1.3). Storage conditions and use-by-end date are part of the label text.

Treatment kit labels will indicate the treatment number (used for treatment allocation and reported in the eCRF). The participant number, visit number, and date of dispensation will be entered manually by the site staff on the treatment box label prior to dispensing.

In case of emergency only, for scheduled or unscheduled visits, the IMP might be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations. Direct-To-Patient (DTP) remains an option and the participant/investigator can refuse this option.

6.3 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP/NIMP/device (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) must be promptly notified to

the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.8).

A potential defect in the quality of IMP/NIMP/device 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 the IMP/NIMP/device and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/NIMP/device to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMP/NIMP/device to be used other than as directed by this clinical trial protocol, or dispose of IMP/NIMP/device in any other manner.

6.4 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

- The randomized intervention kit number list is generated centrally by Sanofi.
- The IMPs are packaged in accordance with this list.
- An interactive response technology (IRT) will generate the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it.
- All participants will be centrally assigned to randomized study intervention using an IRT. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site.
- Study intervention will be dispensed at the study visits summarized in the SoA.
- Returned study intervention should not be re-dispensed to the participants.
- The randomization will be stratified by value of screening HbA1c (<8%, ≥8%), and by use at screening of metformin alone or metformin +SGLT2 (Yes/No).
- 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. Definition of a randomized participant: a participant from screened population who has been allocated to a randomized intervention regardless of whether the intervention was received or not.
- A participant cannot be randomized more than once in the study.
- This is an open-label study because of the existing differences in the type and features of pens used to administer the iGlarLixi and IDegAsp. To compensate for the lack of blinding, the Investigator and the Sponsor will not have access to the data of the primary efficacy parameters (HbA1c, objectively collected and measured at a central laboratory) obtained after baseline visit until the end of the study.
  However, the study team may review the data for the primary efficacy parameter in descriptive statistics with the name of the IMP treatment masked during data review meetings.

6.5 STUDY INTERVENTION COMPLIANCE

- IMP accountability:
  - Intervention units are returned by the participant at each on-site visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract)
  - The Investigator counts the units remaining in the returned packs, and fills in the Intervention Log Form
  - The Investigator records the dosing information on the appropriate page(s) of the eCRF.
  - Also, a diary will be completed by the participant at each IMP administration.
  - The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and intervention log forms
  - Proper placement of tear-off label for accounting purposes
  - For SC injections, participants will be given training during the randomization period to ensure that the participant accepts the route of administration (participant will not be randomized if not comfortable with SC injections).

Compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting of returned units in the pen devices during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of study intervention dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

There will be no access to study intervention or any additional care provided after the end of the study.

6.7 MANAGEMENT OF OVERDOSE

For this study, an overdose is defined as:

- For iGlarLixi: any dose corresponding to a lixisenatide daily dose greater than 40 µg (ie, >40 U [40 U insulin glargine / 40 µg lixisenatide] for 1:1 Pen, >80 U [80 U insulin glargine / 40 µg lixisenatide] for 2:1 Pen)
- For IDegAsp: any dose administration which, in the Investigator's opinion based on clinical judgment, is considered significantly greater than the prescribed dose of insulin,

- An overdose with metformin is defined as any dose greater than 2-fold above the recommended/planned or prescribed dose administrated per day within this study.

In the event of an overdose, the Investigator should:

- Contact the Sponsor immediately.
- Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically.
- Document appropriately in the CRF.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Background therapy

Background treatments metformin ± SGLT-2 inhibitor are considered as NIMPs and will be administered orally according to local labeling. Metformin will be supplied or reimbursed by the Sponsor. An SU, a glinide, an alpha-GI, or a DPP-4 inhibitor, if previously taken, will be stopped before or on the randomization day (V2) for the participants who are eligible for randomization.

Metformin is mandatory background therapy. Daily metformin dose (at least 1000 mg or the maximum tolerated dose) should remain unchanged until the end of treatment period unless there is a specific safety issue related to this treatment.

SGLT-2 inhibitors, if previously taken, should be continued at the stable dose throughout the treatment period unless there is a specific safety issue related to this treatment.

The dose of metformin and SGLT-2 inhibitors is to be reported in the eCRF.

6.8.2 Allowed concomitant therapy

Any therapies or medications other than prohibited concomitant therapy in addition to the study intervention should be kept to a minimum during the study. However, if these are considered necessary for the participant's welfare and are unlikely to interfere with the study intervention, they may be given at the discretion of the Investigator, with a stable dose (when possible).

In the iGlarLixi treatment group, for oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, statins and oral contraceptives, participants should be advised to take those medicinal products at least 1 hour before or 11 hours after study intervention injection. Gastro-resistant formulations containing substances sensitive to stomach degradation should also be administered 1 hour before or 11 hours after injection of iGlarLixi.

Specific treatments, which are ongoing before the study and/or prescribed or changed during the study, must be recorded in the eCRF and source data.

6.8.3 Prohibited concomitant therapy

The following drugs are not permitted during the screening period and the 24-week randomized open-label treatment period:

- Any glucose-lowering agents other than the study interventions, authorized background antidiabetic therapy (metformin ± SGLT-2 inhibitor) and rescue therapy, if necessary.
- Note: Short time use (≤14 days) of short/rapid-acting insulin due to acute illness or surgery (eg, infectious disease) is allowed.
- Systemic glucocorticoids for more than 14days (topical or inhaled applications are allowed).
- Body weight loss drugs which is defined as prescription medications with indication to treat overweight or obesity.
- Using any study interventional drugs other than those specified in this protocol.

After the last administration of study interventions during the study period, any antidiabetic treatments are permitted, as deemed necessary by the Investigator.

6.8.4 Rescue medicine

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Routine central laboratory alerts on HbA1c are required to ensure that glycemic parameter results remain under predefined threshold value. In case HbA1c is above threshold (HbA1C > 8% at Week 12 or later on), the investigator will receive an alert issued by the central laboratory and should ensure that no reasonable explanation exists for insufficient glucose control and in particular that the study treatment is appropriately titrated according to the titration algorithm (up to a maximum of 40 dose steps [40 U insulin glargine / 20 µg lixisenatide] for iGlarLixi group; no upper limit for IDegAsp group), compliance to diet and lifestyle is appropriate, and there is no intercurrent disease, which may jeopardize glycemic control (eg, infectious disease)

If any of the above can reasonably explain insufficient glycemic control, the Investigator should take appropriate actions and retest the central lab HbA1C in 4 weeks at next visit or an unscheduled visit whichever suitable.

If the repeated HbA1c remains above 8% despite appropriate corrective actions or none of the above-mentioned reasons can be found and managed, a rescue therapy can be considered.

- For iGlarLixi group, rescue therapy can be considered if a daily dose >40 dose steps is necessary to decrease HbA1c below the threshold, or if any safety concerns (repeated hypoglycemia, severe gastrointestinal AE, etc) prevent up titration to reach 40 dose steps according to the Investigator's judgment.
- In both iGlarLixi and IDegAsp treatment groups, it is recommended to add one rapid/short-acting insulin; this should be started as a single daily administration to be given at a meal of the day as appropriately at the investigator's discretion.

No other GLP-1 RA or DPP-4 inhibitor or basal insulin, including pre-mixed insulin, should be used as rescue medication in either of the treatment groups.

Once rescue medication is considered as necessary as per the investigator's medical decision, the participant should be scheduled for a **Pre-rescue onsite visit**. Before initiating rescue therapy, all assessments (except 7-point SMPG) planned at the end of treatment visit are to be performed at the pre-rescue visit. After these assessments are completed and rescue therapy initiated, the participant will remain in the study and continue to administer the study treatment (including background therapies). The planned visits and assessments should be performed until the last scheduled visit.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The study intervention should be continued whenever possible. In case the study intervention is stopped, it should be determined whether the stop can be made temporarily; permanent study intervention discontinuation should be a last resort. Any study intervention discontinuation must be fully documented in the eCRF. In any case, the participant should remain in the study as long as possible.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

- In general, Pregnancy will lead to permanent intervention discontinuation.
- Stopping rules described in Appendix 10.5 (Section 10.5) should be applied, if applicable
- Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (please specify, eg after 24 hours) before making a decision of permanent discontinuation of the IMP for the concerned participant.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for end of study visit. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 6, Section 10.6: Contingency measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF.

It is in the interest of the participant to monitor their blood glucose as per the protocol requirement during the temporary discontinuation period, therefore regular determination of SMPG is to be performed and documented. For all temporary treatment discontinuations regardless if related to an AE or other reasons, the duration should be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed. Use of any other antihyperglycemic medication during the time of temporary treatment discontinuation is recorded as concomitant medication with the name and doses recorded in the eCRF.

7.1.4 Rechallenge

Reinitiation of intervention 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(s) in the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met.

For a regional or national emergency declared by a governmental agency that is an epidemic/pandemic (eg COVID-19), the following text should also be considered and added to Appendix 6 (Section 10.6: Contingency measures for a regional or national emergency that is declared by a governmental agency) if applicable: During a regional or national emergency declared by a governmental agency, re-initiation of IMP can only occur once the Investigator has determined, according to his/her best judgement, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg, COVID-19) was unlikely.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 6 (Section 10.6: Contingency measures for a regional or national emergency that is declared by a governmental agency).

Maximal duration of IMP temporary discontinuation to allow IMP restart:

- Up to 4 weeks if before Week 12
- Up to 2 Weeks if after Week 12 and before Week 21
- No re-initiation should be done from Week 21

The investigator may prescribe the re-starting IMP dose at the last dose given before the temporary discontinuation or at an appropriate lower dose based on the investigator's medical judgment after a careful assessment on the participant's glycemic status and the tolerability of the IMP.

Type of antidiabetic treatments that can be used during the temporary IMP discontinuation should be referenced to the respective Rescue therapy:

- No other GLP-1 RA, basal insulin (including pre-mixed insulin) or DPP-4 inhibitor should be used.

7.1.4.1 Study intervention restart or rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study intervention unless:

- Sponsor approval is granted
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for intervention restart/rechallenge is signed by the participant

NOTE: If study intervention was interrupted for suspected intervention-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalization, and jaundice and re-consented before resumption of dosing.

If Sponsor approval to restart/rechallenge participant with study intervention is not granted, then participant must permanently discontinue study intervention and may continue in the study for protocol-specified follow up assessments.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. 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.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented. All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The statistical analysis plan (SAP) will specify how these participants lost to follow-up for their primary endpoints will be considered.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1, (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 200 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 EFFICACY ASSESSMENTS

Planned time points for all efficacy and/or immunogenicity assessments are provided in the SoA.

8.1.1 HbA1c, FPG and fasting C-peptide measurement

For the eligibility and efficacy assessments of the study, HbA1c, FPG and fasting C-peptide are measured by a Chinese national certified central laboratory. Please refer to the flowchart in SoA.

8.1.2 Body weight

Body weight should be obtained with the participant wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study and calibrated on a regular basis as recommended by the manufacturer.

The use of balance scales is recommended; if digital scales are used, testing with standard weights is of particular importance. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The scale should be balanced with both weights at zero and the balance bar aligned. The participant should stand in the center of the platform as standing off-center may affect measurement. The weights are moved until the beam balances (the arrows are aligned). The weight is read and recorded in the eCRF and source data. Self-reported weights are not acceptable; participants must not read the scales themselves.

8.1.3 Self-monitored plasma glucose (SMPG) measurements, glucometer, participant diary and training

Study participants will be supplied with a glucometer, the corresponding supplies (lancets, test strips, etc.), a leaflet, and with diaries at Visit 1 (Week -2) in order to perform self-measurement of plasma glucose and its recording. Participants will be trained how to use the glucometer.

The glucometers should be calibrated according to instructions given in the package leaflet. To ensure the quality and data validity of glucometers, site staff should train participants on how to use control solution to run the control test according to glucometer manual, especially when a new container of test strips is opened; for each on site visit, site staff should check the date/time setting of glucometers and also run a control test. Appropriate documentation should be maintained

Participants will be instructed to bring their glucometers and participant diaries with them to each site visit.

8.1.3.1 Fasting SMPG:

Fasting SMPG will be used by the Investigator and participants if appropriate to titrate and adjust iGlarLixi or IDegAsp dose and to monitor glycemic control. The fasting SMPG should be measured by the participant before the first meal and before the administration of the glucose-lowering agents (IMP or background OAD) once a day from Visit 2 (Week 0, Day 1) to Visit 10 (Week 12), and then at least 3 days per week to the end of treatment Visit 14 (Week 24). The Investigator may decide to request more frequent SMPG if considered necessary for the participant.

Study participants will be instructed to document SMPG values in their diary books. Investigators and site staffs will review and validate the SMPG and the IMP doses in the diary records. During the treatment period, (Day 1 up to Week 24), only **3 fasting** SMPG values per week should be recorded in the eCRF:

- In any week, the 3 fasting SMPG values that are used for IMP dose modification which may include the value on the day of titration.
- If no IMP dose modification occurs, from Day 1 up to Week 12, the 3 fasting SMPG measured in the first 3 days of the week, (preferably 3 consecutive days, eg: Mon-Tues-Wednesday). The same rule is applicable for documentation of fasting SMPG after Week 12 if more than 3 days' SMPG are measured by the participants.

8.1.3.2 Seven-point SMPG Profile:

The 7-point SMPG profile should be measured at the following 7-points: pre-prandial (before starting a meal) and 2 hours postprandial for breakfast, lunch, dinner and at bedtime. Two hours postprandial (breakfast, lunch and dinner) is defined as 2 hours after the start of the meal.

The participants are requested to perform 7-point SMPG profile measurement over a single 24-hour period on 2 different days in the week prior to Visit 2 (Week 0, Day 1), Visit 10 (Week 12), and Visit 14 (Week 24). All SMPG values measured on these days will be recorded in diary and

entered into the eCRF. On the 7-point profile days, information on times of meals, each of SMPG measurement and injection time with doses of IMP should be recorded in the participant diary and entered in the eCRF.

7-Point SMPG is not required for assessments at pre-rescue and premature IMP discontinuation visits.

8.1.3.3 Self-monitored plasma glucose during episodes of hypoglycemia:

Whenever the participant feels hypoglycemic symptoms, plasma glucose should be measured by the participant (or others, if applicable), if possible. Participants should be instructed to measure plasma glucose levels prior to the administration of glucose or carbohydrate intake whenever symptoms due to hypoglycemia is suspected, unless safety considerations necessitate immediate glucose/carbohydrate rescue prior to confirmation.

The SMPG values are to be entered in the participant diary and entered in the eCRF.

Further SMPG: The Investigator may decide to request more frequent SMPG if considered necessary for the participant. The SMPG values are to be entered in the participant diary.

8.1.3.4 Diary

Instruction on how to complete the participant diary on a daily basis will be provided by site staff.

At each on site visit:

- The study site staff reviews the participant diary.
- SMPG values stored in the glucometer memory will be downloaded, printed out, dated, signed and filed into the participant file.

This information will help the Investigator to assess treatment effects, adjust insulin doses and compliance.

Note: The SMPG values recorded into the diary, which have to be entered in the eCRF, have to be checked for consistency with the information downloaded from the glucometer. In case of inconsistency, the reason for inconsistency has to be documented. If needed, the resulting action (eg, training of the participant on correct documentation of the values) is also to be documented. The confirmed values will be entered into eCRF by the Investigator or designee based on the glucometer output values.

The participant diary includes but not limited to the following information:

- Time and dose of IMP (iGlarLixi or IDegAsp) injections.
- Missed IMP injection (including start date and end date).
- Time and value of fasting SMPG measurements.

- Time of start of meals and SMPG measurements as well as plasma glucose values on the day of the 7-point profile.
- Potential changes in metformin treatment and/or SGLT2 inhibitor (if appropriate).
- Adverse events, including signs and symptoms suggesting occurrence of hypoglycemia and local injection site reactions, if any.
- Any problems with the pen-injector.
- Any concomitant medications including prescription and over-the counter drugs.

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AEs which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- A physical examination will include, at a minimum, assessments of the [Cardiovascular, Respiratory, Gastrointestinal and Neurological] systems. Height (at V1) and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous and ongoing illnesses and related to AE during the study.

8.2.2 Vital signs

- Blood pressure (mmHg) should be measured when the participant is quiet and seated and with their arm outstretched in line with mid-sternum and supported. Measurement should be taken under standardized conditions, approximately at the same time of the day, on the same arm, with the same device (after the participant has rested comfortably for at least five minutes) and the values are to be recorded in the eCRF. Both systolic blood pressure and diastolic blood pressure should be recorded.
- Determination of the arm for blood pressure measurements: At screening visit (V1, Week -2) of the screening period, blood pressure has to be measured on both of the arms after 5 minutes in seated position and then again after two minutes in both arms in seated position. The arm with the higher diastolic pressure will be determined at this visit, identifying the reference arm for future measurements throughout the study. The highest value will be recorded in the eCRF (all blood pressure values are to be recorded in the source data).
- Devices for blood pressure measurement should be regularly recalibrated according to manufacturers' instructions.
- Heart rate (bpm) will be measured at the time of the measurement of blood pressure.

8.2.3 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- The investigator should assess the ECG results as normal, abnormal and clinically significant (Y/N) if abnormal. The assessment will be documented in the eCRF.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 3 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.5 Pregnancy testing

- The timepoints for pregnancy testing in WOCBP is defined in the SoA.
- The pregnancy testing would be done by local urine test at study sites.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.6.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs and AEs of special interest, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements

relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- SAEs that are considered expected will be specified in the reference safety information (IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until end of study.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant /pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant /pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Adverse event of special interest

Adverse event of special interest

An AESI is an AE (serious or nonserious) 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 following are considered Adverse events of special interest:

- 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 (see Appendix 3 [Section 10.3]).
  - 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 determined (See Appendix 4 [Section 10.4]).
- 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) and defined as per Section 6.7.
- Increase in alanine transaminase (ALT) more than 3 times the ULN

8.3.7 Hypoglycemia

Hypoglycemia (all, level 1, level 2 and level 3 hypoglycemia) will be assessed starting from randomization (Day 1) and continue until 3 days after the last dose of IMP.

During the study, participants are instructed to document the presence of hypoglycemic episodes in their study diary. The hypoglycemia will be reported in the specific eCRF page with onset date and time, symptoms and/or signs, the SMPG value if available, and the treatment.

Note: If the event fulfills SAE criteria, hypoglycemia will also be reported as an SAE.

Hypoglycemia is categorized according to the ADA 2021 recommendation for hypoglycemia classification (17):

- Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L). Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level <70 mg/dL (3.9 mmol/L) is considered clinically important (independent of the severity of acute hypoglycemic symptoms).
- Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event.
- Level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

Note that "requires assistance" means that the participant could not help himself or herself. Assisting a participant out of kindness, when assistance is not required, should not be considered a "requires assistance" incident.

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP/NIMP/device must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 STUDY PROCEDURES

The visit schedule and procedures/assessments are listed in the Study Flow Chart in Section 1.3. This section provides details for procedures/assessments.

This is an outpatient study and consists of 8 on-site visits and 7 phone-call visits. In addition, optional phone call visits to monitor IMP titration should be scheduled whenever considered necessary by the Investigator.

Participants must be fasting for on-site visits (except Visit 1/ Week 0 and Visit 4/Week 2). The fasting condition is defined as an overnight fast no less than 8 hours that consisted of no food or liquid intake, other than water. The participant should be seen in the morning, at approximately the same time, as far as possible.

Note: If the participant is not fasting at the visits specified above, the blood sample will not be collected and a new appointment should be given to the participant for the following day if possible, with instruction to be fasted.

8.4.1 Screening period (Week -2 to Week 0) and Visit 1

The screening period is up to 2 weeks from screening visit (V1, Week -2) to randomization (V2, Week 0); it can be exceptionally extended up to one additional week.

Only participants who meet the inclusion criteria as noted in Section 5.1 may be screened. It will be the Investigator's responsibility to confirm the diagnosis of T2DM. The background OAD(s) should be continued without dose and type change during the screening period.

If any of the laboratory parameters are not available 2 weeks after screening visit (eg, sample material damaged during transport etc), a retest can be performed. If this is the case (and exceptionally in other situations if justified according to the Investigator's assessment), the screening period can be extended up to one additional week, ie, randomization visit (V2, Day 1) can be scheduled no later than 3 weeks after screening visit (V1, Week -2).

Participants can be re-screened one time before randomization in case of non-evaluable exclusion criteria or in case where original screen failure is due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment. Re-screened participants will be subject to the screening visit procedures/assessments including new informed consent signed and allocation of a new participant number.

For the complete list and contents of procedures/assessments scheduled for the visit, please refer to the Study Flow Chart in Section 1.3 and for detailed description of assessments to Section 8.1, 8.2 and 8.3.

Informed consent:

The participant will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration at Visit 1 (screening visit). Written information will be provided to the participant and must be signed by the participant and Investigator prior to any investigations.

Demography, medical history, and alcohol and smoking habits

Demography, diabetes and medical/surgical history, allergy history, alcohol and smoking habits, and medications Demography data such as birth date and gender will be collected. Collection of diabetes history will include documentation of duration of diabetes, history of microvascular complications (retinopathy, neuropathy, and nephropathy), and history of gestational diabetes if applicable. General medical/surgical history will be recorded. Data for alcohol habits during the last 12 months before screening visit and smoking habits will be collected. Check of previous and/or current medication refers to documentation of medication including glucose-lowering agents and over-the-counter medications. In women of child-bearing potential, the contraceptive method(s) must be documented.

IRT contact

IRT will be contacted for notification of screening and participant number allocation. Please note that it is important to have the IRT contact before any blood sample is drawn because the participant number is given by IRT and it must be reported on the laboratory requisition forms.

Glucometer, participant diary dispensation and training

See Section 8.1.3.

7-Point SMPG

Participants who meet the selection criteria and will return to the study site for Visit 2 should be reminded to perform the 7-point SMPG in two different dates in the week prior to the next visit (Visit 2).

8.4.2 Open-label randomized treatment period (Week 0 to Week 24)

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 period.

The duration of the open-label treatment period is 24 weeks from baseline visit (V2, Week 0) to the end of treatment visit (V14, Week 24). Each participant self-administers IMP once daily during the open-label treatment period (Section 6).

8.4.2.1 Randomization visit (V2, Week 0, Day 1)

For the complete list and contents of procedures/assessments scheduled for the visit, please refer to the Study Flow Chart in Section 1.3 and for detailed description of assessments to Section 8.1, 8.2 and 8.3.

At this visit, the participant must return to the investigational site in the morning in fasting status, i.e., not having any food or drinks (except for water) for at least 8 hours, not having administered metformin and the second OAD (if appropriate) at home.

Patients will visit the site with the blood glucometer and the diary.

Diet and lifestyle counseling

Please see Section 5.3.

Compliance check

Compliance check includes compliance to background OAD metformin and/or SGLT2 inhibitor (if appropriate) and use of glucometer, review of daily of the 7-point SMPG profile and participant diary. If the participant is not compliant enough with the study procedures, the training will be repeated by the site staff.

Any OAD other than metformin and/or SGLT2 inhibitor (if appropriate) will be discontinued on the day of randomization.

IRT contact

After the baseline assessments are completed and eligibility confirmed, the Investigator contacts IRT for randomization. The treatment group (ie, iGlarLixi or IDegAsp) is notified by IRT.

Training on self-injection devices and dispensation of IMP Patients randomized to either treatment group (iGlarLixi or IDegAsp) are instructed by the study staff how to use properly the relevant pen-injector and to store it. Instructions on self-injection technique are also given. Relevant injection pen-injector with the instruction leaflet is dispensed. Training on relevant pen-injector might be repeated if necessary, during the study.

See Section 6 for starting dose and dose adjustment of IM

8.4.2.2 Phone call visits (Visits 3, 5, 7, 9, 11 and 13):

The participant 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. In case of an AE, the participant may be asked to come to the investigational site, as appropriate. A phone call visit can optionally be performed as a clinical visit in case of confirmed hypoglycemia/AE or other reasons.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you miss, change, take or add any medications (including OAD if appropriate) since the last visit
- Did you experience any hypoglycemic events or symptoms?
- Did you experience any possible allergic symptoms, or skin reactions?
- Do you feel comfortable handling the diary, glucometer and IMP injection device or do you need any more explanation?
- Did you adjust IMP since last visit, including missing injection? If appropriate, what is your IMP dose?
- Did you measure any fasting SMPG value < 80 or >100 mg/dL (< 4.4 or > 5.6 mmol/L)?
- The phone visits will also include:
- Adjustment of the dose of IMP (iGlarLixi or IDegAsp) to continue treatment toward the target fasting SMPG ≥80 and ≤100 mg/dL (≥4.4 and ≤5.6 mmol/L).
- Recording of AE and hypoglycemia events (if any).
- Recording of the use or change of any concomitant medication.
- The participant will be instructed to:
- Perform required SMPG measurements.
- Complete the diary on a daily basis.
- Self-inject once daily IMP at the dose prescribed by the Investigator.
- Contact the site in case of occurrence of AE, record the event in the participant diary and return to the site as deemed appropriate. An appointment for subsequent visits (on-site visit or phone call visit) will be given, and patients are reminded to come in fasting if planned at next on-site visit and to bring their glucometer, diary, and IMPs.

8.4.2.3 Onsite visits (Visits, 4, 6, 8, 10, and 12)

For the complete list and contents of procedures/assessments scheduled for the visit, please refer to the Study Flow Chart in Section 1.3 and for detailed description of assessments to Section 8.1, 8.2 and 8.3.

For all onsite visits (except Visit 4/Week 2), participants are instructed to return to the site in the morning in fasting condition with the glucometer, the diary, the used, in-use and unused IMPs.

The IMP iGlarLixi or IDegAsp (if appropriate) and the OAD metformin and SGLT2 inhibitor (if appropriate) will be administrated at the investigational site **after** the fasting blood sample has been drawn.

Compliance check

Compliance check includes compliance to IMP and metformin treatment and SGLT2 inhibitor (if appropriate) and use of glucometer, review of fasting SMPG values, and the 7-point SMPG profile and participant diary. If the participant is not compliant enough with the study, the training will be repeated by the site staff.

The questions listed for phone call visits will also be asked, checked, and discussed with participants at onsite visits.

Upon completion of each on-site visit, an appointment for the next visit (on-site visit or phone call visit) will be made

8.4.2.4 Final on-treatment assessment/end of treatment visit (V14, Week 24)

For the complete list and contents of procedures/assessments scheduled for the visit, please refer to the Study Flow Chart in Section 1.3 and for detailed description of assessments to Section 8.1, 8.2 and 8.3.

The same procedures/assessments including IRT contact as planned at V14 (Week 24) have to be performed in case of prematurely permanent treatment discontinuation.

The IRT has to be contacted in order to register the end of treatment.

An appointment for the post-treatment follow-up phone call visit will be made.

8.4.3 Post-treatment follow-up phone call visit (V15)

Following the last injection of IMP (iGlarLixi or IDegAsp) either as scheduled or prematurely, a post-treatment follow-up phone call visit is performed 3 (-1/+3) days after the end of treatment visit for patients who completed the study or withdrew from the study at the time of the open label IMP discontinuation.

The post-treatment follow-up phone call visit is not performed for patients who prematurely discontinued the open-label IMP treatment and stay in the study.

This visit can be a phone call visit, or an on-site visit in case of ongoing or new AE during the posttreatment period, if necessary. The participant is called by the Investigator or medically qualified designee at certain, previously agreed time point.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you change, take or add any medications since the last visit?
- Did you experience any hypoglycemic symptoms or events?

All reports of hypoglycemic events (if any) or any AEs are recorded. The use or change of any concomitant medications, including rescue therapy, is recorded.

Interactive response technology (IRT) is contacted for notification of the end of study.

8.5 PHARMACOKINETICS

Not applicable

8.6 GENETICS AND/OR PHARMACOGENOMICS

Genetics are not evaluated in this study.

8.7 BIOMARKERS

Biomarkers are not evaluated in this study.

8.8 IMMUNOGENICITY ASSESSMENTS

Not applicable

8.9 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

No biological samples will be collected for future research in this study.

Relating data for future research will be stored for up to 25 years after the end of the study.

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 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).

9.2 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 7 - Populations for analyses

Population	Description
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the treatment 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 will be defined in the SAP and identified before database lock.
Safety	All randomized participants who take at least 1 dose of study intervention. 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 will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

9.3 STATISTICAL ANALYSES

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.3.1 General considerations

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

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

Categorical data will be summarized by treatment group using count and percentage.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from baseline) by scheduled visits will be provided on observed cases, ie, inclusion of only participants having non-missing assessments at a specific visit.

Unless otherwise specified, analyses will be performed by treatment group for baseline, demographics characteristics, prior and concomitant medications.

9.3.2 Analyses of primary endpoint

The primary endpoint is change from baseline to Week 24 in HbA1c. Three estimands addressing different aspects of the trial objective as defined below.

Estimand	Population	Strategy for accounting for intercurrent events	Endpoint	Population level summary
Primary estimand	All randomized participants	Treatment policy strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	Change from baseline to Week 24 in HbA1c*	LS Means difference between treatments
Secondary estimand	All randomized participants	Hypothetical strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	Change from baseline to Week 24 in HbA1c*	LS means difference between treatments
Secondary estimand	Per Protocol	No intercurrent event expected as participants with treatment discontinuation or rescue medication will be excluded from PP population	Change from baseline to Week 24 in HbA1c*	LS means difference between treatments

*For noninferiority testing.

Primary analysis for the primary estimand

Under treatment policy strategy, measurements after treatment discontinuation and initiation of rescue medication will not be considered as missing data.

The primary statistical analysis will be an ANCOVA performed on the ITT population with missing data 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, 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 HbA1c continuous value as covariate. The randomization strata 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.

Sensitivity analyses of primary estimand

The following sensitivity analyses will be performed for the primary estimand.

- The primary endpoint will be analyzed using a mixed-effect model with repeated measures (MMRM), under the missing at random framework. The model will include treatment, previous OADs, visit, treatment-by-visit interaction as fixed effects, and baseline HbA1c value as continuous covariate. The randomization strata of HbA1c can 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 scheduled visits.

Primary analysis for the secondary estimands

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

A mixed-effect model with repeated measures (MMRM), under the missing at random framework, will be performed for both secondary estimands. The model will include treatment, previous OADs, visit, treatment-by-visit interaction as fixed effects, baseline HbA1c value as continuous covariate. The randomization strata of HbA1c can 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.

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 patients with treatment discontinuation or rescue medication, as well of patients with missing assessment will be excluded from PP population, no missing data handling method is planned for this analysis.

Subgroup analyses of the primary estimand

Depending on the data availability, 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 years).
- Gender (Male, Female).
- Baseline BMI level (<24, ≥24 to <28, ≥28 kg/m2).
- Randomization strata screening HbA1c (<8%, ≥8%).
- Randomization strata treatment at screening with metformin alone or metformin +SGLT2 (Yes/No).
- Baseline fasting C-peptide level by quartiles.

Other subgroup analyses may be explored and will be described in the SAP.

Other sensitivity analyses may be explored. The detailed sensitivity analysis method will be described in the SAP.

9.3.3 Analyses of secondary endpoints

9.3.3.1 Key secondary endpoints analysis

See Section 3 for key secondary efficacy endpoints. Two estimands addressing different aspects of the trial objective as defined below.

Estimand	Population	Strategy for accounting for intercurrent events	Endpoint	Population level summary
Primary estimand	All randomized participants	Treatment policy strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	Change from baseline to Week 24 in: • HbA1c* • Body weight	LS mean difference between treatments
			If a participant at Week 24 achieves: • HbA1c < 7% • HbA1c < 7% and no body weight gain • HbA1c < 7% and no body weight gain and no hypoglycemia (defined as ADA level 1. 2 or 3)	Odds ratio between treatments
Secondary estimand	All randomized participants	Hypothetical strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	Change from baseline to Week 24 in: • HbA1c* • Body weight	LS mean difference between treatments

*For superiority testing.

Analyses of the secondary efficacy endpoints will be performed using the ITT.

Descriptive statistics (Number, mean, SD, median, minimum, and maximum) will be provided by treatment for body weight at the scheduled visits.

Change from baseline in body weight will be analyzed using the same approach as the primary endpoint (ANCOVA with MI or MMRM) to compare iGlarLixi with IDegAsp. The model will include treatment group, randomization strata of HbA1c and previous OAD and corresponding baseline for that endpoint. Details will be provided in the SAP.

All categorical key secondary efficacy endpoints defined in Section 3 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 CI at the specified significance level. 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. Details of the logistic model will be discussed in the SAP.

9.3.3.2 Other secondary endpoints

See Section 3 for other secondary efficacy endpoints. Unless otherwise specified, other secondary endpoints will be analyzed in the treatment policy framework using the ITT population.

Population	Strategy for accounting for intercurrent events	Endpoint	Population level summary
All randomized participants	Treatment policy strategy for both intercurrent events: • Treatment discontinuation • Initiation of rescue medication	Change from baseline to Week 24 in: • FPG • 7-point SMPG • Fasting C-peptide	LS mean difference between treatments
		If a participant at Week 24 achieves: • HbA1c < 7% and no hypoglycemia (any hypoglycemia ADA level 1. 2 or 3) • HbA1c < 7% and no clinically relevant hypoglycemia (any hypoglycemia ADA level 2 or 3) • Initiation of rescue medication	Odds ratio between treatments

Descriptive statistics (Number, mean, SD, median, minimum, and maximum) will be provided by treatment for FPG, 7-point SMPG and fasting C-peptide at the scheduled visits. Descriptive statistics (Number, mean, SD, median, minimum, and maximum) will be provided by treatment for total insulin dose.

For continuous secondary endpoints, such as change from baseline in FPG, 7-point SMPG and fasting C-peptide, they will be analyzed using the same approach as the primary endpoint to compare iGlarLixi with IDegAsp. The model will include treatment group, randomization strata of HbA1c and the corresponding baseline for that endpoint. Details will be provided in the SAP.

Other secondary categorical efficacy endpoints defined in Section 3 will be analyzed using a logistic regression model same with the key secondary categorical endpoints. Details of the logistic model will be discussed in the SAP.

9.3.4 Multiplicity adjustment

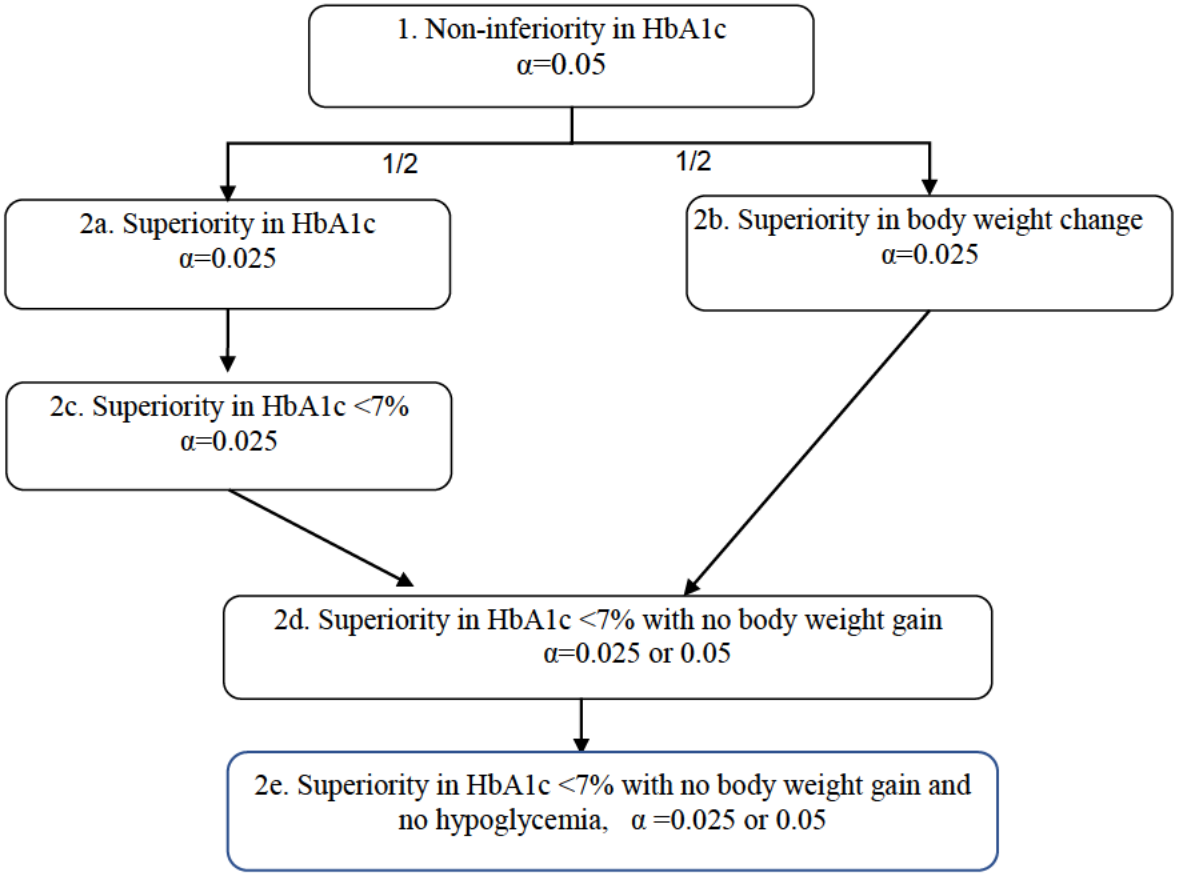
Multiplicity adjustment: to control overall Type I error at 0.05 level (2-sided), a gate-keeping procedure will be used. Two families of hypothesis testing will be established: family 1 of primary and family 2 of key secondary hypotheses. For the primary endpoint (change from baseline to Week 24 in HbA1c), 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 2.

- 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 2 - Graphical illustration of the gate-keeping procedure



9.3.5 Safety analysis

All safety analyses will be performed on the Safety Population as defined in Section 9.2 using the following common rules:

The following definitions will be applied to laboratory parameters, vital signs and electrocardiograms (ECGs).

- The potentially clinically significant abnormality (PCSA) values for clinical laboratory tests, vital signs and ECGs are defined as abnormal values considered medically important by the Sponsor's Global Pharmacovigilance and Epidemiology department. PCSA criteria for parameters not cited in the protocol as safety parameters will not be analyzed.
- Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated);
- PCSA criteria will determine which participants had at least one PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such participants will be the numerator for the on-treatment PCSA percentage.

- 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

9.3.5.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the time between the date of the informed consent and the first injection of open-label IMP.
- TEAEs: AEs that developed, worsened or became serious during the time from the first injection of open-label IMP up to 3 days (1 day for hypoglycemia) after the last injection of IMP, regardless of initiation of rescue medication. The 3-day interval is chosen based on the half-life of the IMP (approximately 5 times the half-life of lixisenatide).
- Post-treatment AEs: AEs that developed, worsened or became serious during the time from 4 days (2 days for hypoglycemia) after last injection of open-label IMP (after the on-treatment period) to end of study.

Analysis of all adverse events

Adverse event incidence table will be sorted by System Organ Class (SOC) internationally agreed order and decreasing frequency of preferred term (PT) for the treatment group, the number (n) and percentage (%) of participants experiencing at least one TEAE. In case of equal frequencies of PTs within a SOC, the alphabetic order will be applied. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages is the safety population within each treatment group.

Summaries of all TEAEs in each treatment group may include:

- The overview of AEs, summarizing number (n) and percentage (%) of participants with any
- TEAE;
- Study drug related TEAE;
- Treatment emergent SAE;
- Study drug related treatment emergent SAE;
- Treatment emergent AESI
- Study drug related treatment emergent AESI
- TEAE leading to death;
- Study drug related TEAE leading to death;

- TEAE leading to permanent treatment discontinuation.
- Study drug related TEAE leading to permanent treatment discontinuation.
- The number (n) and percentage (%) of participants with at least one TEAE by primary SOC, HLGT, HLT, and PT;
- Summary of TEAEs by maximal severity, presented by primary SOC and PT;
- Summary of TEAEs related to open-label IMP, presented by primary SOC and PT.

A detailed listing of TEAE summaries will be provided in the SAP.

Death and treatment emergent SAEs will be summarized and presented as number (n) and percent (%) of participants in each treatment group.

9.3.5.2 Analyses of hypoglycemia

Analyses of hypoglycemia will be performed, including any hypoglycemia, level 1 hypoglycemia, level 2 hypoglycemia, level 3 hypoglycemia, hypoglycemia occurred at any time of the day, hypoglycemia occurred nocturnally.

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.

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, it's 95% CI and p-value 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.

9.3.5.3 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

For laboratory variables, vital signs and ECG variables, descriptive statistics for results and changes from baseline will be provided for each planned visit during the on-treatment period. The central laboratory measurements for safety parameters will be analyzed.

Analyses according to PCSA

The number (n) and percentage (%) of participants with PCSA at any evaluation during the on-treatment period will be summarized for each parameter within each treatment group. The summaries will include participants in the safety population who have at least one parameter to be analyzed during the on-treatment period. When the PCSA definition involves the change from the baseline value, participants need also to have a baseline value to be included in the summaries.

Tabular and graphical methods may be used to present the results for parameters of interest.

Listings will be provided with flags indicating the PCSA values.

9.3.5.4 Study treatment duration and compliance

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

The extent of study treatment exposure will be assessed by the duration of treatment exposure during the study.

The duration of treatment exposure will be the total number of days of administration of the open-label IMP, regardless of unplanned intermittent discontinuations. The duration of IMP exposure will be calculated as:(Date of the last open-label IMP injection – Date of the first open-label IMP injection) + 1.

The number (n) and percentage (%) of participants randomized and exposed to the open-label IMP will be presented by categories of cumulative exposure for each treatment group in the safety population. The time periods of interest will be defined in the SAP.

Descriptive statistics of duration of treatment exposure (number, mean, SD, minimum, median, and maximum) and cumulative exposure in participant-years will also be presented by treatment group in the safety population.

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. Compliance rate (%)=total number of days with IMP injection/ planned number of days with IMP injection*100. A given administration will be considered noncompliant if the participant did not take the planned dose of treatment as required by the protocol. For example, if participants miss one of the two injections in any day of the premixed insulin treatment, that day will be considered noncompliant. No imputation will be made for participants with missing or incomplete data.

Treatment compliance will be summarized by treatment group using mean, SD, median, and range for the safety population. In addition, the percentage of participants who have <60%, ≥60% to <80%, ≥80% to ≤100%, and >100% compliance will be summarized by treatment group.

9.4 INTERIM ANALYSES

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator Brochure, [IDFU] and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
- The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and

- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants or their legally authorized representative, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

Participants who are rescreened are required to sign a new ICF.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 6 (Section 10.6: Contingency measures for a regional or national emergency that is declared by a governmental agency).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other phamaceutical company members of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required

by the National Medical Products Administration (NMPA) in its guidance "Implementation of Drug Clinical Trial Information Registration and Disclosure" ("Notification No. 28"), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.6 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the study "CRF completion instruction".
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study "Monitoring guidelines".
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is considered the first act of recruitment of a participant and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development

- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in below Table 8 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 10.5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations [(for instance, when participants with known acquired immunodeficiency syndrome (AIDS)-related illness or known HIV disease requiring antiviral treatments need to be excluded, an HIV serology testing at screening is mandatory for German participants)].

Table 8 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices: • MCV • MCH • %Reticulocytes
	White blood cell (WBC) count with differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose [Indicate if fasting, or nonfasting]
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase[b]
	Total and direct bilirubin
	Total protein Amylase Lipase Calcitonin
Pregnancy testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • All study-required laboratory tests will be performed by a central laboratory
Other study specific tests	• FPG, HbA1c, fasting C-peptide, SMPG

Laboratory tests	Parameters

NOTES:

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 [Liver Chemistry Stopping Criteria] and Appendix 5 (Section 10.5) [Liver and other safety: Suggested actions and follow-up assessments [and study intervention rechallenge guidelines]]. All events of [insert criteria related to ALT, bilirubin, INR etc] which may indicate severe liver injury (possible Hy's Law) must be reported to [Sponsor] in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

b If alkaline phosphatase is elevated, consider fractionating.

c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant/participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants/ participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/ parental /LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant/participant's parent(s)/LAR(s) will be collected during interview with the participants/participant's parent(s)/LAR(s) and by review of available medical records at the next visit.
- Solicited AEs are predefined local [at the injection site] and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - 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
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out participant setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) **which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.**

e) Is a congenital anomaly/birth defect

f) Is a suspected transmission of any infectious agent via an authorized medicinal product

g) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- 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 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × 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

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

  "Severe" is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the "Investigator Site File".

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the "Investigator Site File".

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

Woman of childbearing potential (WOCBP): A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

10.4.2 Contraception guidance

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

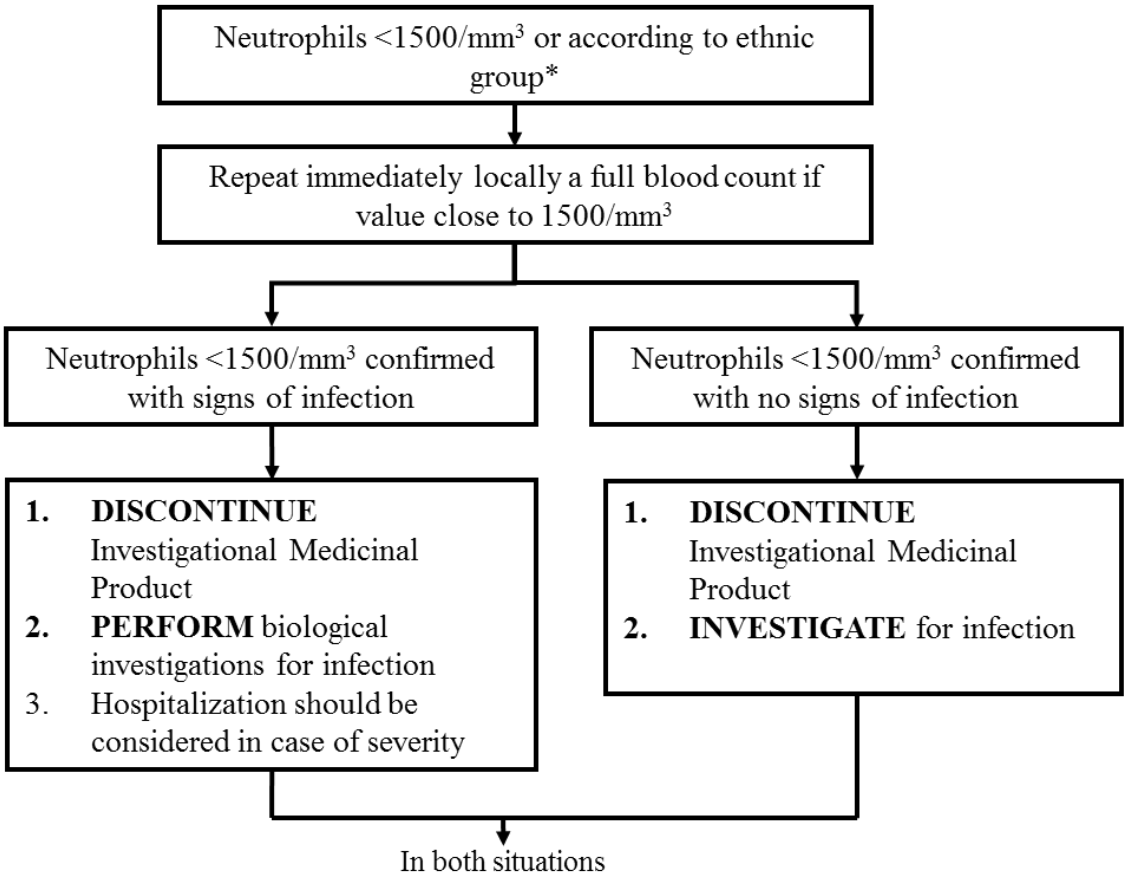
Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 APPENDIX 5: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

NEUTROPENIA

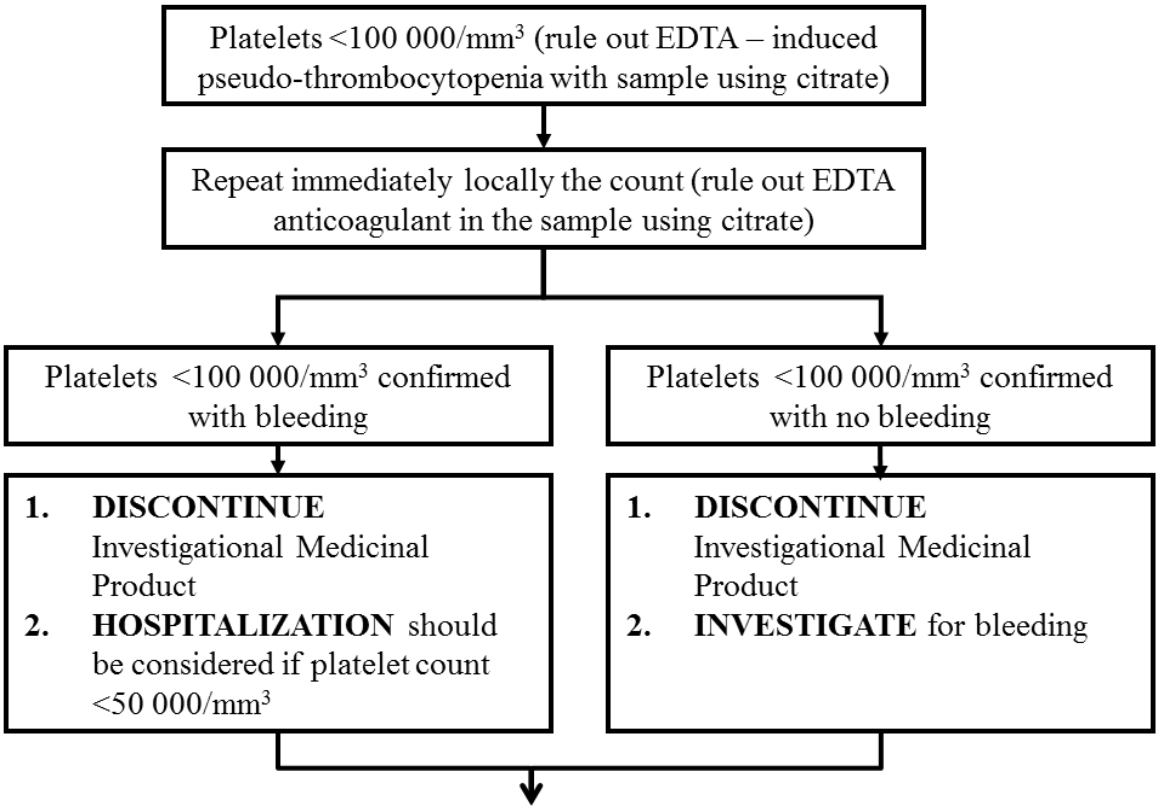


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs is met.

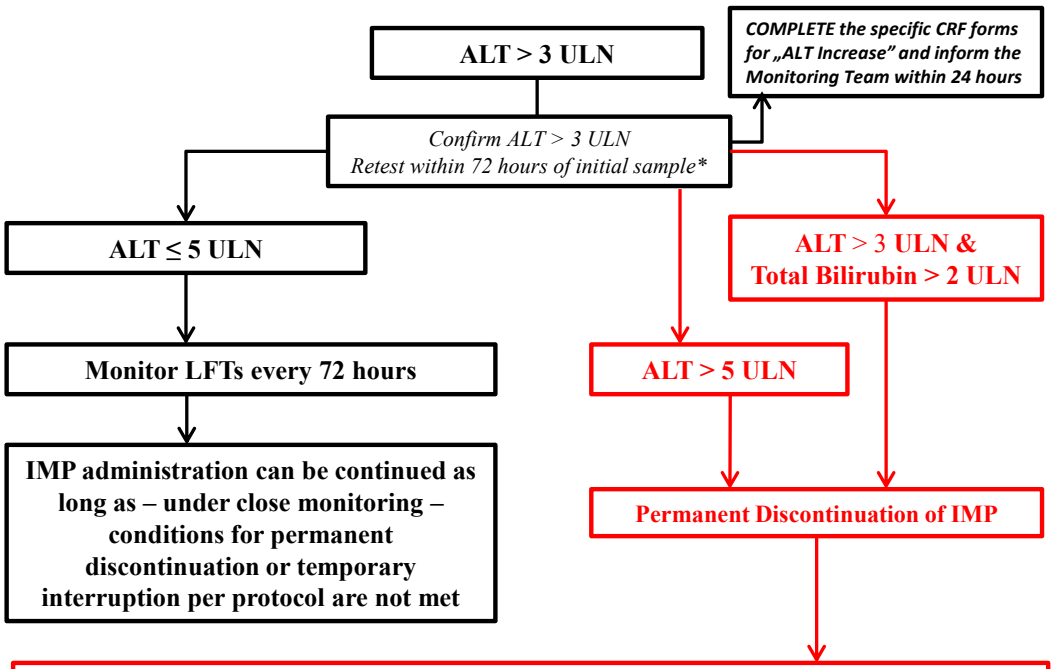
THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about alcohol habits, any drug intake including quinine (drinks), heparin administration, aspirin, immunotherapy, etc.
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Locally:
     - Bleeding time and coagulation tests (INR or PT, aPTT, D-Dimers)
     - Infectious serologies to be performed according to clinical symptoms / medical history
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
7. **DECISION** for bone marrow aspiration to be taken in specialized unit
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs is met.

INCREASE IN ALT

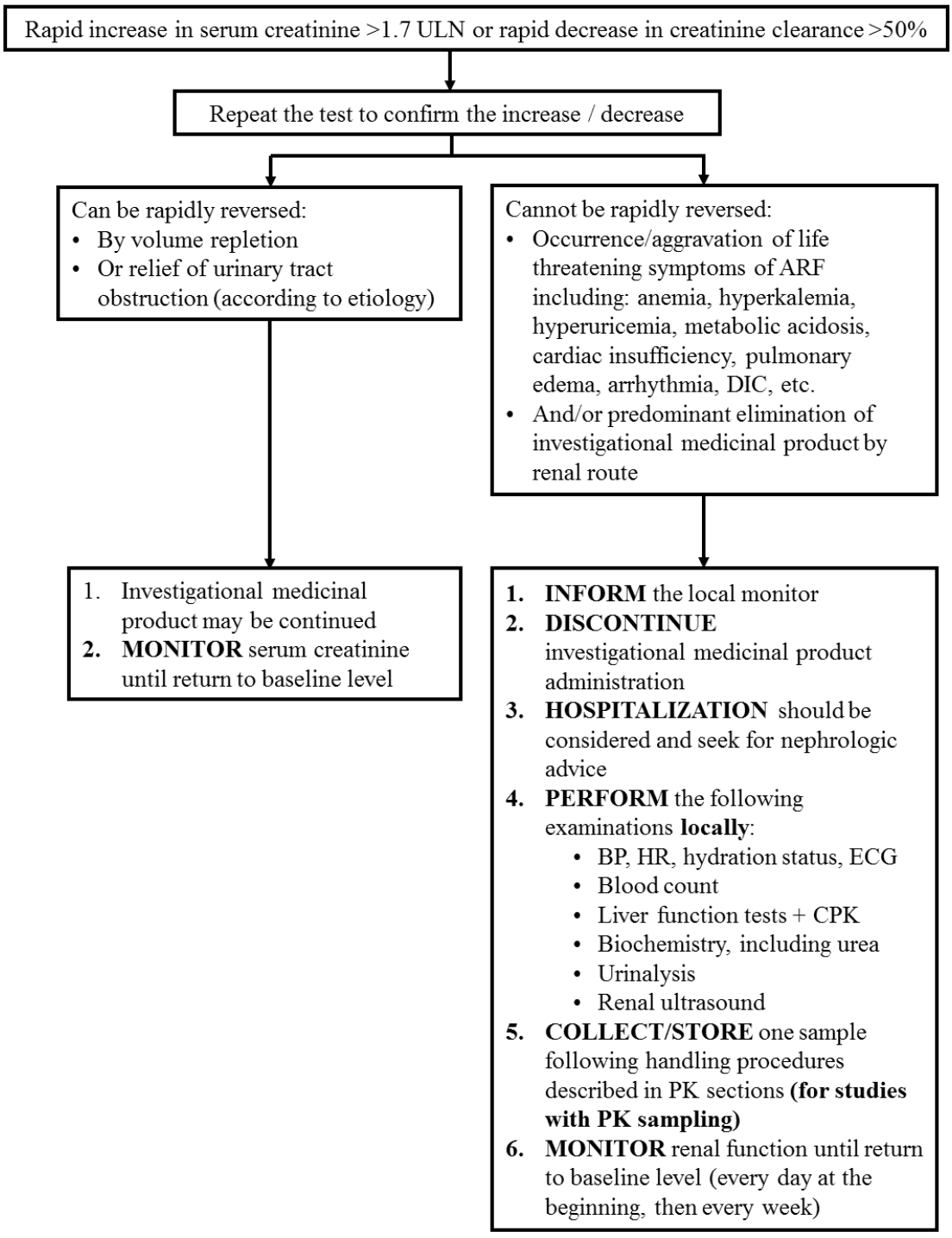


In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** consulting with hepatologist
6. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
7. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
8. **FREEZE** serum sample (5ml x 2)
9. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

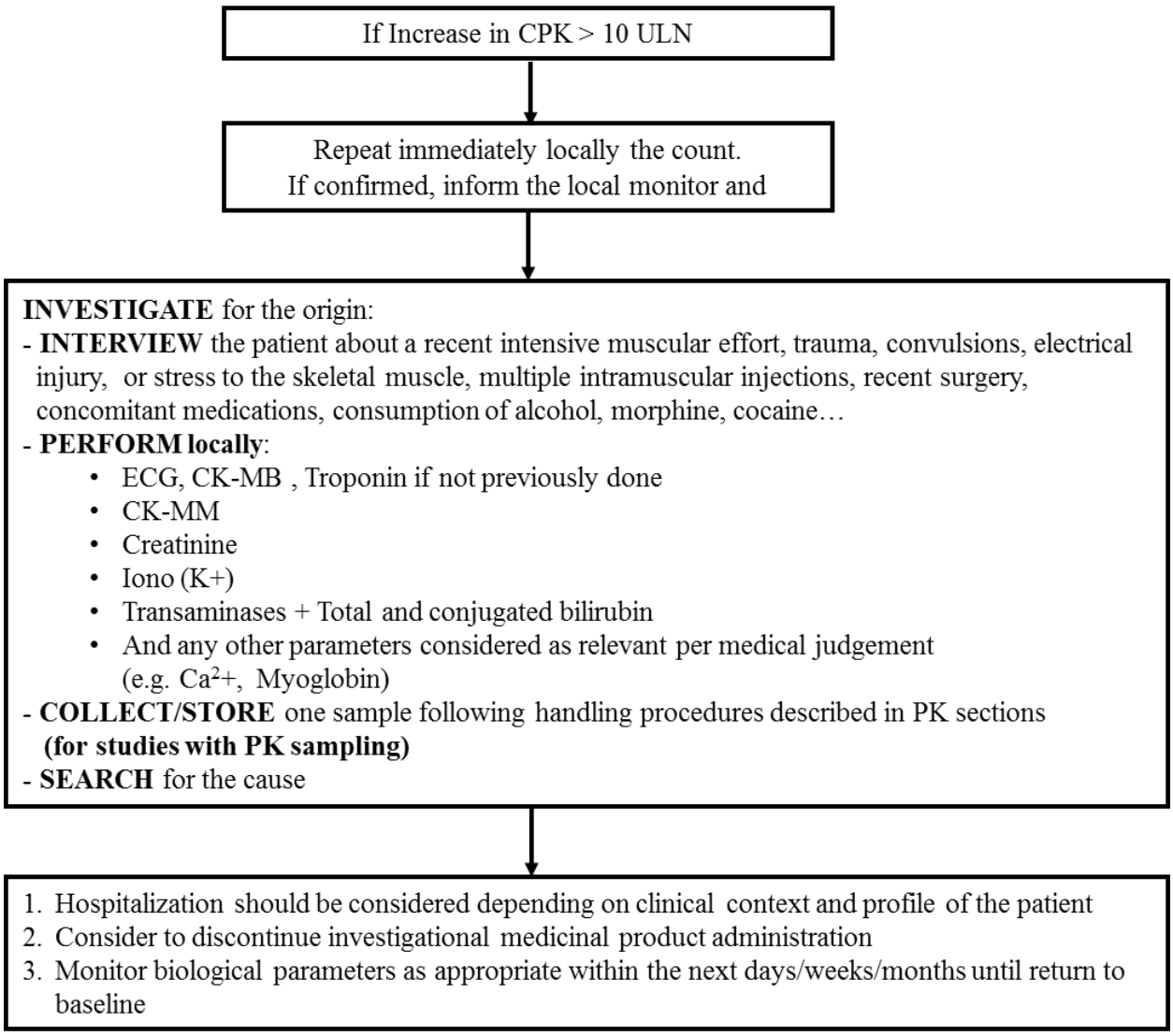
*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
Note:
"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
See Section 10.3 for guidance on safety reporting.
Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs is met.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs is met.

10.6 APPENDIX 6: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below and in sections for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/randomization/administration of study intervention may be [temporarily delayed/halted.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data.
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.

Informed consent: For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participants or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg. study visit delays/treatment extension, use of local labs).

- Contingencies implemented due to emergency will be documented.

10.7 APPENDIX 7: ABBREVIATIONS

AEs:	adverse events
AESIs:	adverse events of special interest
DTP:	direct-to-patient
ICF:	informed consent form
IMPs:	investigational medicinal products
NIMPs:	non-investigational medicinal products
NMPA:	National Medical Products Administration
PCSA:	potentially clinically significant abnormality
SAEs:	serious adverse events
SMPG:	self-monitored plasma glucose
SUSAR:	suspected unexpected serious adverse reaction

10.8 APPENDIX 8: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

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