

Clinical Study Protocol

Study Title:	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Clinical Trial Evaluating the Efficacy and Safety of IBI362 in Chinese Adults with Type 2 Diabetes Inadequately Controlled by Diet and Exercise Alone (DREAMS-1)
Protocol No.:	CIBI362A301
Version Date and No.:	Version 4.0/March 14, 2024
Product Name:	IBI362
Study Phase:	Phase 3
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, 215213, China
Sponsor Contact:	

SPONSOR SIGNATURE PAGE

Study Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Clinical Trial Evaluating the Efficacy and Safety of IBI362 in Chinese Adults with Type 2 Diabetes Inadequately Controlled by Diet and Exercise Alone (DREAMS-1)

Protocol No.: CIBI362A301

Job title	Name(s)	Signature	Date
Clinical Development Senior Director			
Biostatistics Associate Director,			

Investigator Signature Page

Study Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Study Evaluating the Efficacy and Safety of IBI362 in Chinese Patients with Type 2 Diabetes Inadequately Controlled by Diet and Exercise (DREAMS-1)

Protocol No.: CIBI362A301

This protocol is a confidential document of Innovent Biologics (Suzhou) Co., Ltd. I have read through and fully understand this protocol and will conduct this study in accordance with its requirements and Good Clinical Practice. Furthermore, I will abide by the ethics principles in Declaration of Helsinki and GLP and applicable laws and regulations during the study. I promise not to disclose any confidential information in this study to any third party without the written consent of Innovent Biologics (Suzhou) Co., Ltd.

Instructions for Investigator:

Please sign and date this signature page, print Investigator's name and title, site name/address, and send it back to Innovent Biologics (Suzhou) Co., Ltd. after signing.

I have read the full content of this study protocol and promise to carry out this study as required:

Signature of Investigator: _____ Date _____

Print Name: _____

Investigator Title: _____

Tel.: _____

Site Name/Address: _____

Synopsis

Protocol Number	CIBI362A301
Sponsor	Innovent Biologics (Suzhou) Co., Ltd
Study Drug	IBI362
Active Ingredient	IBI362
Study Title	A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Study Evaluating the Efficacy and Safety of IBI362 in Chinese Patients with Type 2 Diabetes Inadequately Controlled by Diet and Exercise (DREAMS-1)
Study Phase	Phase 3
Study Objectives	Primary objective: - To validate that IBI362 is superior to placebo in terms of the change in glycosylated hemoglobin A_{1c} (HbA_{1c}) level from baseline at week 24. Key secondary objectives: - To validate that the efficacy of IBI362 in glycemic control and weight loss is superior to placebo at week 24. Other secondary objectives: - To evaluate the effects of IBI362 in cardiovascular and metabolic parameters; - To assess patient-reported outcomes (PROs); - To evaluate the safety and tolerability of IBI362; - To evaluate the pharmacokinetics (PK) of IBI362.
Study Endpoints	Primary endpoint: - Change from baseline in HbA_{1c} at week 24. Key secondary endpoints: - At week 24: - Proportion of participants achieving HbA_{1c} <7.0% from baseline; - Proportion of participants achieving HbA_{1c} <7.0% and weight loss of ≥5% from baseline; - Proportion of participants achieving weight loss ≥5% from baseline; - Percentage change from baseline in body weight. Other secondary endpoints: <u>Efficacy endpoints</u> - At week 48: - Change in HbA_{1c} from baseline;

	– Proportion of participants achieving HbA_{1c} <7.0% from baseline; – Proportion of participants achieving weight reduction ≥5% from baseline; – Proportion of participants achieving HbA_{1c} <7.0% and weight reduction ≥5%; – Percentage change from baseline in body weight. • At weeks 24 and 48: – Proportion of participants achieving HbA_{1c} ≤6.5% and HbA_{1c} <5.7%; – Changes in fasting plasma glucose (FPG) from baseline; – Change in serum 1,5-anhydroglucitol (1,5-AG) from baseline; – Change in 7-point fingertip blood glucose from baseline; – Changes in waist circumference and body-mass index (BMI) from baseline; – Absolute change in body weight from baseline; – Proportion of participants achieving weight loss ≥10% from baseline; – Change in systolic and diastolic blood pressure from baseline; – Blood lipid [total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG)] levels from baseline; – Change in blood uric acid (UA) level from baseline; – Changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels from baseline; – Change from baseline in urine albumin-to-creatinine ratio; – Change in patient-reported outcome (PRO) questionnaire scores from baseline: Diabetes Treatment Satisfaction Questionnaire (DTSQ) score; European Quality of Life-5 Dimensions (EQ-5D-5L); – Changes in HOMA2-B and HOMA2-IR from baseline. <u>Safety endpoints:</u> • The incidence and severity of adverse events (AEs) and their correlation with the study drug. • Changes in vital signs, physical examinations, laboratory tests, and electrocardiograms (ECG), as well as the incidence of abnormal parameters from baseline. • To evaluate the immunogenicity of IBI362.
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	<u>Pharmacokinetic and pharmacodynamic endpoints:</u> • To evaluate the population PK characteristics of IBI362, including but not limited to: time to maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), area under curve (AUC), volume distribution (V), half-life ($T_{1/2}$), and clearance (CL). • To assess the changes in PD parameters (fasting insulin and fasting C-peptide) at different time points before and after administration.
Study Design	This is a multi-center, randomized, double-blind, placebo-controlled phase 3 trial evaluating the efficacy and safety of IBI362 in type 2 diabetes (T2D) adults with inadequately controlled diet and exercise alone. This trial aims to enroll approximately 300 T2D participants who do not reach the target HbA_{1c} after at least 2 months of diet and exercise alone. Participants are required to maintain control of diet and exercise throughout the study. The entire study period includes a 4-week screening period, a 6-week lead-in period, a 24-week double-blind treatment period, a 24-week study extension period, and a 4-week safety follow-up period. <u>Screening period:</u> Relevant examinations were performed to check the inclusion and exclusion criteria and determine the eligibility of the participants. <u>Lead-in period:</u> Eligible participants will enter the lead-in period, during which anyone using hypoglycemic medication before randomization is ineligible and withdraw from the trial. During the lead-in period, participants will be trained on disease monitoring [e.g., self-monitoring of blood glucose (SMBG)], disease management procedures, study diary cards, and study procedures. Participants should return to the hospital within the last week of the lead-in period for retesting of HbA_{1c}, FPG or fasting serum glucose (FSG), body weight, etc., and assessment of randomization criteria. <u>Double-blind treatment period:</u> Participants who met the randomization criteria were randomized into IBI362 4.0 mg group, IBI362 6.0 mg group, or placebo group in a 1:1:1 ratio. The randomization stratification factors were $HbA_{1c} < 8.5\%$ or $HbA_{1c} \geq 8.5\%$ prior to randomization (V3). During the double-blind treatment period, IBI362 and placebo will be blinded to Investigator, participants, and Sponsor. The dosing regimens are as follows: • IBI362 4.0 mg group: Subcutaneous injection once weekly (QW); the starting dose was IBI362 2.0 mg, and after 4 weeks of

	consecutive administration, the dose was increased to IBI362 4.0 mg, and the administration lasted for 20 weeks. • IBI362 6.0 mg group: Subcutaneous injection QW; the starting dose was IBI362 2.0 mg. After 4 weeks of consecutive administration, the dose was increased to IBI362 4.0 mg. After 4 weeks of consecutive administration, the dose was further increased to IBI362 6.0 mg for 16 weeks. • Placebo group: Subcutaneous injection QW for 24 consecutive weeks. <u>Study extension period:</u> After completing the double-blind treatment period, the participants will be transitioned to the extension period of the study with the following dosing regimens: • IBI362 4.0 mg group: Subcutaneous injection QW; IBI362 4.0 mg, consecutive administration for 24 weeks. • IBI362 6.0 mg group: Subcutaneous injection QW; IBI362 6.0 mg, consecutive administration for 24 weeks. • Placebo group: Switching to IBI362 treatment with the starting dose of IBI362 2.0 mg. After 4 weeks of consecutive administration, the dose was adjusted to IBI362 4.0 mg. After 4 weeks of consecutive administration, the dose was increased to IBI362 6.0 mg for 16 weeks. Dose modification in the double-blind treatment period and the extension period: Dose resumption after dose reduction is not allowed. Management of gastrointestinal adverse events: During the treatment period, if Investigator assesses that the participant is still intolerant to gastrointestinal adverse events after dietary pattern adjustment or symptomatic treatment, dose interruption may be considered: • Up to one less dose is allowed every 4 weeks; • If a participant's gastrointestinal AEs resolve after dose interruption, Investigator should resume the dose before dose interruption, or initiate the next dose level at investigator's discretion according to the participant's condition; the total treatment period remains 48 weeks. If a participant is still unable to tolerate gastrointestinal AEs despite the above measures, Investigator may discuss with Sponsor and decide to increase the frequency of dose interruptions or discontinue the treatment.
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	<u>Safety follow-up period:</u> During the safety follow-up period, Investigator can decide the hypoglycemic regimen for participants at his/her discretion (GLP-1 receptor agonists and DPP4 inhibitors are prohibited).
Number of Samples	Approximately 300 participants
Inclusion Criteria	Participants must meet <u>all</u> of the following inclusion criteria to be included in the study: 1. Diagnosis of T2D for at least 2 months according to the 1999 WHO criteria (see Appendix 6). 2. Aged ≥ 18 years at the time of signing the informed consent form. 3. Participants with inadequate glycemic control after diet and exercise alone within 2 months prior to screening, with $7.5\% \leq \text{HbA}_{1c} \leq 10.5\%$ tested at a local laboratory at screening. 4. BMI $\geq 23 \text{ kg/m}^2$ at screening. 5. Able to maintain a stable diet and exercise lifestyle during the study. 6. Participants who voluntarily sign the informed consent form and agree to strictly follow the requirements of this protocol.
Exclusion Criteria	Participants meeting <u>any</u> of the following exclusion criteria must be excluded from the study: 1. Participants who, judged by Investigator, may be allergic to components of the study drug or similar drugs. 2. Body weight change $>5\%$ (complaint) within 12 weeks prior to screening. 3. Use of any of the following medications or therapies prior to screening: 1) Have used any hypoglycemic drug within 2 months prior to screening; have used ≥ 3 hypoglycemic drugs in combination more than 2 months prior to screening. 2) Use of GLP-1R (glucagon-like peptide-1 receptor) agonist or GLP-1R/GCGR (glucagon receptor) agonist or glucose-dependent insulintropic polypeptide receptor (GIPR)/GLP-1R agonist or GIPR/GLP-1R/GCGR agonist within 2 months prior to screening; participants who have discontinued the above drugs due to lack of efficacy or intolerance more than 2 months prior to screening are also excluded. 3) Use of insulin for diabetes control within 3 months prior to screening, except for short-term (cumulative use ≤ 14 days) use of insulin in an acute state, such as acute illness, hospitalization, or

	elective surgery. Last treatment with insulin was <14 days from the screening day in any case. 4) Use of drugs with weight loss efficacy within 2 months prior to screening or planned use during the trial, such as semaglutide, beinaglutide, liraglutide, orlistat, sibutramine hydrochloride, phenylpropanolamine, chlorphenazone, phentermine, lorcaserin hydrochloride, phentermine, phentermine/topiramate, diethylpropion, and naltrexone/bupropion. 5) Use of Chinese herbal medicines, other traditional medicines, and health products with hypoglycemic effect within 2 months prior to screening. 6) Currently receiving chronic (>2 weeks) systemic glucocorticoids therapy or having used glucocorticoids within 4 weeks prior to screening (excluding topical, ophthalmic, intranasal, or inhaled administration). 7) Current use of central nervous system stimulants, excluding beverages containing caffeine, at screening. 8) Have participated in other clinical trials and received study treatment within 3 months prior to screening. 9) History of alcohol and drug abuse at screening. Average weekly alcohol intake: more than 21 units for males and more than 14 units for females (1 unit = 360 mL of beer, or 150 mL of red wine, or 45 mL of distilled spirits/liquor). 4. History or evidence of any one of the following diseases: 1) Previously diagnosed with type 1 diabetes mellitus (T1D) [including latent autoimmune diabetes in adults (LADA)]. 2) Two or more episodes of ketoacidosis, diabetic hyperosmolar state, or lactic acidosis within 6 months prior to screening. 3) History of severe hypoglycemic episodes within 6 months prior to screening, defined as neuroglycopenic symptoms requiring assistance of another person for recovery, or hypoglycemia unawareness or insufficient awareness of hypoglycemic symptoms. Participants who, judged by Investigator, are unable to communicate and understand symptoms of hypoglycemia and appropriate treatment should also be excluded from this study. 4) History of acute or chronic pancreatitis, or blood amylase or lipase $>2.0 \times \text{ULN}$, or fasting TG $\geq 5.64 \text{ mmol/L}$ (500 mg/dL) at screening.
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	5) History of gastroparesis or bariatric surgery, or abnormal gastric emptying clinically significant judged by Investigator. 6) History or presence at screening of proliferative diabetic retinopathy, or diabetic macular edema, or nonproliferative diabetic retinopathy requiring urgent treatment. 7) Acute and chronic hepatitis (except chronic hepatitis B), symptoms and signs of other liver diseases, or ALT $>3.0 \times \text{ULN}$ (ALT $>5.0 \times \text{ULN}$ for non-alcoholic fatty liver disease), or AST $>3.0 \times \text{ULN}$, or total bilirubin (TBIL) $>2.0 \times \text{ULN}$. 8) History or family history of medullary thyroid cancer, multiple endocrine neoplasia (MEN) 2A or 2B. 9) Hyperthyroidism or hypothyroidism confirmed by clinical evaluation and/or abnormal thyroid stimulating hormone (TSH) levels that in Investigator's judgment would increase subject risk; except for participants on stable-dose thyroid hormone replacement therapy for at least 2 months with normal thyroid function currently and expected to maintain consistent dosage throughout the study period. 10) A previous definitive diagnosis of autonomic neuropathy manifested by urinary retention, resting tachycardia, orthostatic hypotension, or diabetic diarrhea. 11) History of acute myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention (except diagnostic angiography), transient ischemic attack (TIA), cerebrovascular accident, severe arrhythmia (such as ventricular fibrillation, ventricular flutter, atrial fibrillation, atrial flutter, third-degree atrioventricular block, etc.), and pre-excitation syndrome within 6 months prior to screening; or a previous diagnosis of decompensated heart failure or Grade III or IV heart failure identified by the New York Heart Association (NYHA). 12) A 12-lead ECG showing heart rate $<50 \text{ bpm}$ or $>100 \text{ bpm}$, or ECG indicative of active cardiac disease, or ECG abnormalities judged by Investigator as potentially interfering with ECG result interpretation during follow-up (with specific exclusion of QTcF $>500 \text{ ms}$). 13) Poorly controlled hypertension at screening, with systolic blood pressure (SBP) $\geq 160 \text{ mmHg}$ or diastolic blood pressure (DBP) $\geq 100 \text{ mmHg}$; or antihypertensive drugs (dose or type of drugs)
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	modified within 30 days before screening; evidence of renal artery stenosis, or labile blood pressure (including postural hypotension, etc.). 14) Active or untreated malignant tumors within 5 years prior to screening, or in remission of clinical malignant tumors (except for patients with basal cell carcinoma and squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the prostate, or papillary thyroid carcinoma without recurrence after surgery). 15) Serum calcitonin ≥ 35 ng/L (pg/mL) at screening. 16) Glomerular filtration rate eGFR < 45 mL/min/1.73 m² at screening, estimated using the CKD-EPI formula (see Appendix 2). 17) History of atopic reactions (clinical manifestations of severe or multiple allergies) or clinically significant history of multiple or severe drug allergies, or intolerance to topical glucocorticoids, or severe post-treatment hypersensitivity reactions (including but not limited to erythema multiforme, linear immunoglobulin A dermatitis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis). 18) History of or evidence of human immunodeficiency virus (HIV) infection, positive HIV antibody, positive hepatitis C virus (HCV) antibody, or positive syphilis antibody at screening. 19) Hepatitis B surface antigen (HBsAg) positive and hepatitis B virus DNA copy number ≥ 1000 IU/mL (drug-naïve participants) or receiving anti-hepatitis B virus (HBV) treatment at screening. 20) History of organ transplantation (except corneal transplantation), or preparing for organ transplantation. 21) Presence of serious active and uncontrolled physical conditions or medical history, which may be in a dangerous state during the use of the study drug or interfere with the interpretation of the efficacy and safety data of this study, as judged by Investigator at screening. 22) History of or presence of psychiatric disorders at screening that, in Investigator's judgment, render the participant unsuitable for participation in this study. 23) Blood donation and/or blood loss ≥ 450 mL or bone marrow donation, blood transfusion or severe blood loss within 3 months prior to screening, or the presence of hemoglobinopathy, hemolytic anemia, sickle cell anemia, or hemoglobin < 110 g/L (males) or
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	<100 g/L (females) at screening, or any other known factor that may interfere with HbA_{1c} test results. 5. Pregnant or lactating women, or men or women of childbearing potential who are unwilling to use contraception during the entire study period until 8 weeks after the end of the study. 6. Participants who are not suitable for participating in this study due to any other factors that may affect the efficacy or safety evaluation of this study, as judged by Investigator.
Randomization Criteria	HbA_{1c}, FPG, or FSG, and body weight should be retested at V3 in the lead-in period, and participants should meet all of the following randomization criteria before randomization: 1. Local laboratory testing $7.0\% \leq \text{HbA}_{1c} \leq 10.5\%$. 2. Local laboratory testing FSG or FPG ≤ 15.0 mmol/L. 3. BMI ≥ 23 kg/m² and weight change of $\leq 5\%$ during the lead-in period (V2 and V3).
Study Drug / Administration	The study drugs are all administered via abdominal subcutaneous injection QW, with the dosing regimen as follows: • IBI362 4.0 mg group: 2.0 mg, 4-week administration + 4.0 mg, 44-week administration. • IBI362 6.0 mg group: 2.0 mg, 4 weeks + 4.0 mg, 4 weeks + 6.0 mg, 40 weeks. • Placebo group: 24-week administration in the double-blind treatment period, with consistent administration and dosage form with IBI362. During the extension period of the study, participants will switch to receive IBI362 2.0 mg for 4 weeks + 4.0 mg for 4 weeks + 6.0 mg for 16 weeks.
Estimands	Treatment-policy estimand: This estimand represents the efficacy regardless of the completion of planned protocol-required therapies and the use of rescue therapy for persistent hyperglycemia. Efficacy estimand: This estimand represents the efficacy before premature discontinuation of study intervention or rescue treatment for persistent hyperglycemia. In the application for marketing registration, the analysis will be mainly based on the treatment estimand. If the primary endpoint is reached under the treatment estimand, a positive result will be considered for this study, and the application for marketing registration of IBI362 will be submitted. The analysis based on the efficacy estimand will be used as supporting evidence

	for non-registration purposes, such as publication of research papers. No multiplicity adjustment will be made between the two estimands.
Statistical Methods	Sample size: Assuming that HbA_{1c} in the IBI362 4.0 mg and IBI362 6.0 mg groups after 24 weeks of continuous treatment is decreased by 1.6% and 1.7%, respectively, and HbA_{1c} in the placebo group is decreased by 0.3% with a standard deviation of 1.2% and $\alpha = 0.05$ (two-sided), this study plans to enroll 300 participants with no more than 330 participants. The participants will be randomized into 3 treatment groups in a 1:1:1 ratio, namely the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group. The stratification factor is HbA_{1c} level prior to randomization (V3) (HbA_{1c} <8.5% or HbA_{1c} ≥8.5%). With a power of 99% or greater, statistical superiority of either IBI362 dose group to the placebo group can be observed. Hypothesis test: Takeing the primary endpoint as an example: At week 24, change in HbA_{1c} in the IBI362 group from baseline: μ_{IBI362}; At week 24, change in HbA_{1c} from baseline in the placebo group: μ_{placebo}; $H_0: \mu_{\text{IBI362}} \geq \mu_{\text{placebo}}$ $H_a: \mu_{\text{IBI362}} < \mu_{\text{placebo}}$ Superiority of IBI362 group vs. placebo group will be tested in the order of the following endpoints at $\alpha = 0.05$. • Change in HbA_{1c} from baseline at week 24 (IBI362 6.0 mg vs. placebo); • Change in HbA_{1c} from baseline at week 24 (IBI362 4.0 mg vs. placebo); • Proportion of participants with HbA_{1c} <7.0% at week 24 (IBI362 6.0 mg vs. placebo); • Proportion of participants with HbA_{1c} <7.0% at week 24 (IBI362 4.0 mg vs. placebo); • Proportion of participants with HbA_{1c} <7.0% and a ≥5% decrease in body weight from baseline at week 24 (IBI362 6.0 mg vs. placebo); • Proportion of participants with HbA_{1c} <7.0% and a ≥5% decrease in body weight from baseline at week 24 (IBI362 4.0 mg vs. placebo); • Proportion of participants with a ≥5% weight loss from baseline at week 24 (IBI362 6.0 mg vs. placebo);

	• Proportion of participants with a $\geq 5\%$ weight loss from baseline at week 24 (IBI362 4.0 mg vs. placebo); • Percent change in body weight from baseline at week 24 (IBI362 6.0 mg vs. placebo); • Percent change in body weight from baseline at week 24 (IBI362 4.0 mg vs. placebo); The efficacy differences between each IBI362 dose group and the placebo group at each endpoint will be compared sequentially. If the test of this endpoint is significant ($p < 0.05$), it can be considered that this IBI362 dose group is statistically superior to the placebo group at this endpoint, and the test of the next endpoint can be performed. If the test result is not significant ($p \geq 0.05$), it is considered that the statistical superiority of IBI362 dose group over the placebo group on this endpoint is not established, and no test on any endpoint after this endpoint sequence will be performed. All between-group comparisons were performed in parallel at the two estimands, $\alpha = 0.05$. No multiplicity adjustment will be performed between the two estimands. Statistical methods: <u>Analysis of efficacy</u> • Analysis of primary and secondary endpoints by continuous variables under the treatment estimand Analysis of covariance (ANCOVA) will be used, with treatment group and randomization stratification factors as fixed effects in the model, and the baseline value of the corresponding parameter as a covariate. The mean values of the corresponding parameters of the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group and their 95% confidence intervals (CIs) will be calculated. The between-treatment difference estimates, corresponding standard errors, 95% CIs, and corresponding p values of each IBI362 dose group compared with the placebo group will be provided. Intercurrent events are premature discontinuation of treatment and use of rescue therapy for any reason. Intercurrent events are addressed using the treatment policy strategy, i.e., data collected after the intercurrent event is continued to be used. If there is any missing data in the data collected after the occurrence of the intercurrent event, multiple imputation (MI) will be performed using the data of participants in the same group who have experienced the intercurrent event but have collected the measurement results of the corresponding indicators.
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	For missing values not caused by intercurrent events, MI will be performed using the data of participants in the same group from which the corresponding index measurement results are collected. Analysis of the primary and major secondary endpoints Continuous measures under the efficacy estimand The mixed model repeated measure (MMRM) will be used, with the treatment group, visit, treatment group-by-visit interaction, and randomization stratification factors as the fixed categorical effects, and the baseline value of the corresponding indicator as the covariate. The corrected least squares estimates and their 95% CIs of the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group will be calculated, respectively, and the estimated between-treatment differences, corresponding standard errors, 95% CIs, and corresponding p-values of the two IBI362 dose groups vs. the placebo group will be provided. Intercurrent events were premature discontinuation of treatment and use of rescue therapy for any reason. Data after the occurrence of an intercurrent event will not be included in the analysis, and the intercurrent event will be handled using a hypothetical strategy, assuming that no participants in the study experience drug efficacy in the event of an intercurrent event. Data after the occurrence of intercurrent events will be imputed using the missing at random (MAR) method built into the MMRM model SAS. Missing data not caused by intercurrent events will also be imputed using the MAR method built into the MMRM model of SAS. Analysis of categorical secondary endpoints under the treatment-policy estimand Logistic regression will be used, with treatment group and randomization stratification factor as fixed effects and corresponding baseline measurement as a covariate. The odds ratio (OR) and its 95% CI of IBI362 4.0 mg group and IBI362 6.0 mg group vs. placebo group, as well as the corresponding p value, will be provided. The estimated between-treatment differences in the achievement rate of two IBI362 dose groups vs. the placebo group and its 95% CI will be calculated. The achievement rate for each group will be calculated and the corresponding 95% CI will be provided. The intercurrent event is premature discontinuation of treatment and use of rescue therapy for any reason. Intercurrent events will be addressed using the treatment-policy strategy, i.e., data collected after the intercurrent event will continue to be used. For missing data collected after the occurrence of intercurrent events, MI will be performed using the data of participants in the
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	same group who experience intercurrent events but have available outcome measurements. and then the compliance will be derived based on the imputed continuous variables. For missing values not caused by intercurrent events, MI will be performed using the data of participants in the same group from which the corresponding index measurement results are collected. The compliance status is then derived based on the imputed continuous variable. Analysis of categorical key secondary endpoints under the efficacy estimand Logistic regression will be used with treatment group and randomization stratification factor as fixed effects and corresponding baseline measurement as a covariate. The OR and its 95% CI as well as the corresponding p value of IBI362 4.0 mg group and IBI362 6.0 mg group vs. placebo group will be provided. The estimated between-treatment difference in the achievement rate of two IBI362 dose groups vs. the placebo group and its 95% CI will be calculated. The compliance status will be calculated for each group and the corresponding 95% CI will be provided. Intercurrent events refer to premature discontinuation of treatment and use of rescue therapy for any reason. Data after the occurrence of an intercurrent event will not be included in the analysis, and the intercurrent event will be handled using a hypothetical strategy, assuming that no participants in the study experience drug efficacy in the event of an intercurrent event. Data occurring after the intercurrent event will be assumed to be MAR, using MI under the MAR mechanism, and then the compliance status will be derived based on the imputed values. Missing data that are not caused by intercurrent events will be assumed to be MAR, using MI under the MAR mechanism, and then its compliance will be derived based on the imputed values. <u>Safety analysis</u> Adverse event The number and percentage of participants with AEs in each category will be summarized by system organ class, preferred term, and severity of AEs in the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory tests, vital signs, and ECG For hematology, blood biochemistry, vital signs, ECG, and other indicators, the measured values and changes before and after administration will be described using mean $\pm$ standard deviation, maximum, minimum, and median by treatment group, and the normal and abnormal changes before and
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	after administration were described using potentially clinically significant abnormalities (PCSAs) or cross-classification tables. • Immunogenicity The immunogenicity of IBI362 will be summarized and analyzed. • Other Death cases will be listed in detail. Hypoglycemic events will be summarized by treatment group. • Pharmacokinetic Parameters
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Schedule of Activities

Table 1. Schedule of Activities

	Screening period ¹	Lead-in period		Double-blind treatment period								Study extension period					Safety follow-up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	
Visit time (week, W)	-10~-6	-6	-1~0	0	1	4	5	8	9	12	20	24 (Primary Endpoint)	28	32	40	48 (End of treatment period)	52	
Visit window (days)	NA	+3	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	
Signing of ICF	X																	
Assignment of screening number	X																	
Inclusion / Exclusion Criteria Assessment	X																	

	Screening period ¹	Lead-in period		Double-blind treatment period								Study extension period					Safety follow-up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	
Visit time (week, W)	-10~-6	-6	-1~0	0	1	4	5	8	9	12	20	24 (Primary Endpoint)	28	32	40	48 (End of treatment period)	52	
Visit window (days)	NA	+3	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	
Assignment of Randomization Number ³				▲														
CLINICAL ASSESSMENTS																		
Demographic data	X																	
Medical history / treatment history (including history of smoking and alcohol use)	X																	

	Screening period ¹	Lead-in period		Double-blind treatment period								Study extension period					Safety follow-up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	
Visit time (week, W)	-10~-6	-6	-1~0	0	1	4	5	8	9	12	20	24 (Primary Endpoint)	28	32	40	48 (End of treatment period)	52	
Visit window (days)	NA	+3	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	
Vital Signs ⁴	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X											X					X	X
Height	X																	
Weight ⁵	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X
Waist Circumference ⁶	X	X		X		X		X		X	X	X	X	X	X	X	X	X
12 -Lead ECG ⁷	X			X						X		X				X	X	X
Dilated Funduscopy ⁸	X																	
Injection Site Reaction ⁹				X	X	X	X	X	X	X	X	X	X	X	X			

	Screening period ¹	Lead-in period		Double-blind treatment period								Study extension period					Safety follow-up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	
Visit time (week, W)	-10~-6	-6	-1~0	0	1	4	5	8	9	12	20	24 (Primary Endpoint)	28	32	40	48 (End of treatment period)	52	
Visit window (days)	NA	+3	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diabetes education, glucometer dispensing, SMBG training, and self-injection training		X																
Distribution of diary cards		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

	Screening period ¹	Lead-in period		Double-blind treatment period								Study extension period					Safety follow-up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	
Visit time (week, W)	-10~-6	-6	-1~0	0	1	4	5	8	9	12	20	24 (Primary Endpoint)	28	32	40	48 (End of treatment period)	52	
Visit window (days)	NA	+3	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	
Diary card retrieval and review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Remind the participant of seven-point fingertip blood glucose ¹⁰		X									X				X			
Review 7-point fingertip blood glucose			X	X								X				X		

	Screening period ¹	Lead-in period		Double-blind treatment period								Study extension period					Safety follow-up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	
Visit time (week, W)	-10~-6	-6	-1~0	0	1	4	5	8	9	12	20	24 (Primary Endpoint)	28	32	40	48 (End of treatment period)	52	
Visit window (days)	NA	+3	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	
Dispensing of study drugs				X	X	X	X	X	X	X	X	X	X	X	X			
Study Drug Administration ¹¹				X	X	X	X	X	X	X	X	X ¹¹	X	X	X			
Return of study drug						X	X	X	X	X	X	X	X	X	X	X		X
Assess study drug compliance						X		X		X	X	X	X	X	X	X		
Laboratory tests																		
Blood / Urine Pregnancy Test ¹²	X		X							X		X					X	X

	Screening period ¹	Lead-in period		Double-blind treatment period								Study extension period					Safety follow-up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	
Visit time (week, W)	-10~-6	-6	-1~0	0	1	4	5	8	9	12	20	24 (Primary Endpoint)	28	32	40	48 (End of treatment period)	52	
Visit window (days)	NA	+3	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	
HbA1c ¹³	X		X	●		●		●		●	●	●		●	●	●		●
FPG ¹⁴			X	●		●		●		●	●	●		●	●	●		●
1,5-AG ¹⁵				●								●				●		●
Local Laboratory Tests ¹⁶	X			X						X		X				X		X
Central Laboratory Test ¹⁷				●						●		●				●		●
Urine Albumin / Creatinine Ratio (UACR) ¹⁸				●						●		●				●		●

	Screening period ¹	Lead-in period		Double-blind treatment period								Study extension period					Safety follow- up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	
Visit time (week, W)	-10~-6	-6	-1~0	0	1	4	5	8	9	12	20	24 (Primary Endpoint)	28	32	40	48 (End of treatment period)	52	
Visit window (days)	NA	+3	NA	NA	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7	
eGFR (CKD- EPI) ¹⁹	X			●						●		●				●		●
Viral serological testing ²⁰	X																	
Thyroid Function ²¹	X																	
Immunogenicity Test ²²				●		●		●				●		●		●	●	●
PK ²³				●						●		●				●		●
Participant-Reported Outcomes ²⁴																		
DTSQ				X								X				X		X
EQ-5D-5L				X								X				X		X

Notes:

1. If the screening examinations are more than 14 days from the lead-in date, HbA1c, vital signs, hematology, blood biochemistry, blood lipids, urinalysis, ECG, amylase, lipase, calcitonin, thyroid function, and serum pregnancy tests should be repeated.
2. If the participant is unwilling or unable to continue participating in the study for any reason, the early withdrawal visit should be performed at the next theoretical visit; if the participant withdraws from the study early and is not administered at the visit, the visit can be regarded as the early withdrawal visit. Participants who discontinue the treatment for any reason are required to complete the early discontinuation visit 1 week (± 3 days) after the last dose, as detailed in [Section 4.6.2](#). If the participant has received the local laboratory tests specified in the early treatment discontinuation/early withdrawal visit within two weeks before the early treatment discontinuation or early withdrawal from the study, the tests do not need to be repeated. If a participant withdraws from the treatment early, a diary card should be distributed; if the participant withdraws early, no diary card needs to be distributed.
3. Randomization criteria should be assessed at V3 (see [Section 4.3](#)). Only participants who meet the criteria can proceed to the subsequent trial procedures, and participants who do not meet the criteria will be treated as lead-in failures. The duration of the lead-in period should be ≥ 6 weeks. The time interval between the date of randomization (V3) and the date of randomization (V4): If ≤ 7 days, the lead-in is considered successful even if no retest is required; if > 7 days, the relevant indicators involved in the randomization criteria should be retested to confirm that they meet the randomization criteria before the lead-in is considered successful. At V4, all baseline examinations (including vital signs, weight, waist circumference, laboratory tests, and questionnaires) must be completed before randomization. The first dose of the study drug will be given after all other visit items and randomization are completed.
4. Time window for vital signs measurement: Vital signs measurement should be completed before administration (except for visits without administration). Blood pressure and pulse should be measured twice on the same arm. After the first blood pressure measurement, it should be measured again after an interval of 1 min. See [Section 6.2.2.2](#) for details.
5. Weight: Participants should be fasting, after urination, and take off their coat at each measurement. Participants should use a calibrated weight scale that is within the validity period of calibration at each measurement, and avoid strenuous exercise before measurement. Weight in kg, rounded to 1 decimal place.
6. Waist circumference: (1) Upright stance with relaxed shoulders and abdomen, normal breathing, and feet spaced 25–30 cm apart; (2) Anatomical landmark: Mid-axillary line at the midpoint between the anterior superior iliac spine (ASIS) and the lower border of the 12th rib; (3) A measuring tape placed horizontally around the abdomen at the designated level, maintaining snug contact with the skin without indentation; (4) No voluntary contraction or protrusion of abdominal muscles. Measurement recorded at the end of a natural exhalation, with values expressed in centimeters (cm) and rounded to one decimal place (e.g., 69.3 cm).
7. 12-lead ECG indicators include: RR interval, PR interval, heart rate (HR), QT interval, and QTcF ($QTcF = QT/RR^{0.33}$). If the participant has ECG abnormalities, Investigator can perform additional ECGs according to the actual situation.

8. All participants will undergo dilated funduscopy and/or optical coherence tomography (OCT) by professionals (if the participant can provide a fundus examination report within 3 months before screening, the fundus examination will not be repeated during the screening period) to rule out proliferative diabetic retinopathy, diabetic macular edema, or nonproliferative diabetic retinopathy requiring urgent treatment. If the conditions for pupil dilation are not met, fundus photos or ultra-widefield fundus photos can be used instead.
9. Injection site reactions: The skin and mucous membranes at the injection site should be specially observed for abnormalities within 1 h after each administration, including but not limited to swelling, flushing, ecchymosis, pruritus, induration, pain (except for prickling and transient pain) at the injection site.
10. Seven-point fingertip blood glucose (before breakfast, 2 h $\pm$ 30 min after breakfast, before lunch, 2 h $\pm$ 30 min after lunch, before dinner, 2 h $\pm$ 30 min after dinner, and before bedtime) should be completed within 2 weeks before V4, V12, and V16. For each seven-point fingertip blood glucose measurement, the measurements on two non-consecutive days should be collected. At least 1 complete set of seven-point fingertip blood glucose of one day should be provided before V4, V12, and V16. Participants are encouraged to monitor 4-point fingertip blood glucose every two weeks (before three meals and before bedtime).
11. Administration once weekly with a minimum of ≥ 5 days between doses and skip dose if < 5 days between doses. Administration at non-visit weeks may be performed at home. Administration in the extension period will be started at V12 (if the target dose has not been titrated at V12 visit, these participants need to titrate to the target dose before starting administration in the extension period).
12. Blood/urine pregnancy test is applicable to women of childbearing potential and is required at V1. In addition to the time points specified for visits, Investigator may also perform additional blood/urine pregnancy tests based on clinical judgment.
13. Central laboratory HbA_{1c} test: The blood sampling points are V4, V6, V8, V10, V11, V12, V14, V15, and V16. If the participant discontinues treatment/withdraws early from the study, 1 sample should be collected at the early treatment discontinuation/early withdrawal visit. 2 mL of whole blood will be collected at each visit point. Refer to the central laboratory manual for details. In addition, HbA_{1c} test should be performed at V1 and V3 by the local laboratory.
14. FPG: The blood sampling points of the central laboratory samples are V4, V6, V8, V10, V11, V12, V14, V15, and V16. If a participant discontinues treatment/withdraws early, 2 mL of peripheral blood will be collected at the time of early treatment discontinuation/early withdrawal. The collection should be performed under fasting conditions at each visit point. Detailed procedures refer to the central laboratory manual. At V3, the test will be performed in a local laboratory. If this item is not available in the local laboratory, FSG can be used instead.
15. 1,5-AG: The blood sampling points of central laboratory samples are V4, V12, and V16. If a participant discontinues treatment/withdraws early, 2 mL of peripheral blood will be collected at the time of early treatment discontinuation/early withdrawal. The collection should be performed under fasting conditions at each visit point. Detailed procedures refer to the central laboratory manual.
16. Local laboratory tests include:
 - (1) Hematology: white blood cell count, red blood cell count, platelets, hemoglobin concentration, hematocrit, and white blood cell differential count (neutrophils, basophils, eosinophils, monocytes, and lymphocytes);

- (2) Blood biochemistry: ALT, AST, total bilirubin, direct bilirubin, albumin, total protein, glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, serum potassium, serum sodium, serum calcium, serum chloride, uric acid, urea (or urea nitrogen), creatinine, and creatine kinase (CK);
 - (3) Blood lipids: TC, TG, HDL-C, and LDL-C;
 - (4) Blood amylase and blood lipase (at least blood amylase should be tested if the conditions of the study site are limited);
 - (5) Urinalysis: urine pH, urine protein, urine glucose, urine ketone body, urine red blood cells, and urine white blood cells;
 - (6) Calcitonin (If calcitonin cannot be detected due to the limited conditions of the study site, options include: 1) calcitonin test should be performed at other participating study sites of CIBI362A301 in the same city; 2) calcitonin test should be performed at a tertiary hospital other than the participating study site of CIBI362 A301 in the same city).
17. The blood sampling points for central laboratory test are V4, V10, V12, and V16, and 7.5 mL of peripheral blood should be collected at each visit point under fasting conditions. If a participant discontinues treatment/withdraws early, samples will be collected at the time of early treatment discontinuation/early withdrawal visit. These include:
- (1) Blood biochemistry: ALT, AST, uric acid, and creatinine;
 - (2) Blood lipids: TC, TG, HDL-C, and LDL-C;
 - (3) Blood amylase and blood lipase;
 - (4) Calcitonin;
 - (5) Fasting insulin, fasting C-peptide.
18. 5 mL of urine samples will be collected, and the urine albumin/creatinine ratio (mg/g) will be calculated based on the results of urine albumin and urine creatinine.
19. eGFR was calculated using the CKD-EPI formula (see [Appendix 2](#)), and the results were recorded rounded to 1 decimal place.
20. Virus serology test: including HIV antibody, hepatitis B test (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), hepatitis C (HCV) antibody, and syphilis antibody. If the hepatitis B surface antigen is positive, hepatitis B virus DNA test should be performed.
21. Thyroid function parameters include: thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4).
22. Immunogenicity sampling points: pre-dose at V4, V6, V8, V12, and V14, and at V16 and V17. If a participant discontinues treatment/withdraws early, an immunogenicity sample should be collected at the time of early treatment discontinuation/withdrawal visit. If a participant experiences an injection site reaction or allergic reaction, it is recommended that the participant come to the hospital to collect immunogenicity blood samples at the following time points as far as possible: at the beginning of the event, at the end of the event, and 30 days ($\pm$ 3 days) after the end of the event. A total of 5 mL of whole blood will be collected at each blood sampling time point. Refer to the central laboratory manual for details.

23. PK sampling time points: pre-dose and $4 \text{ h} \pm 1 \text{ h}$ post-dose at V4; within 2 h pre-dose at V10 and V12, and at V16. If a participant discontinues treatment/withdraws early, 1 PK sample should be collected at the time of early treatment discontinuation/withdrawal visit. 3 mL of whole blood will be collected at each blood sampling time point. Refer to the central laboratory manual for details.
24. Participants should complete the relevant questionnaires after confirming that there is no discomfort in the fasting state or there are no adverse effects on their physical and mental state after completing all the visit contents.

In this study, "fasting" refers to fasting for at least 8 h. The drug can only be administered after the completion of fasting blood sampling.

During the study period, missing visits, out-of-window visits, dose interruptions, etc. due to COVID-19 and other epidemics should be clearly recorded in the medical record.

● Performed at the central laboratory, ▲ indicates the assignment of random number.

Study Design

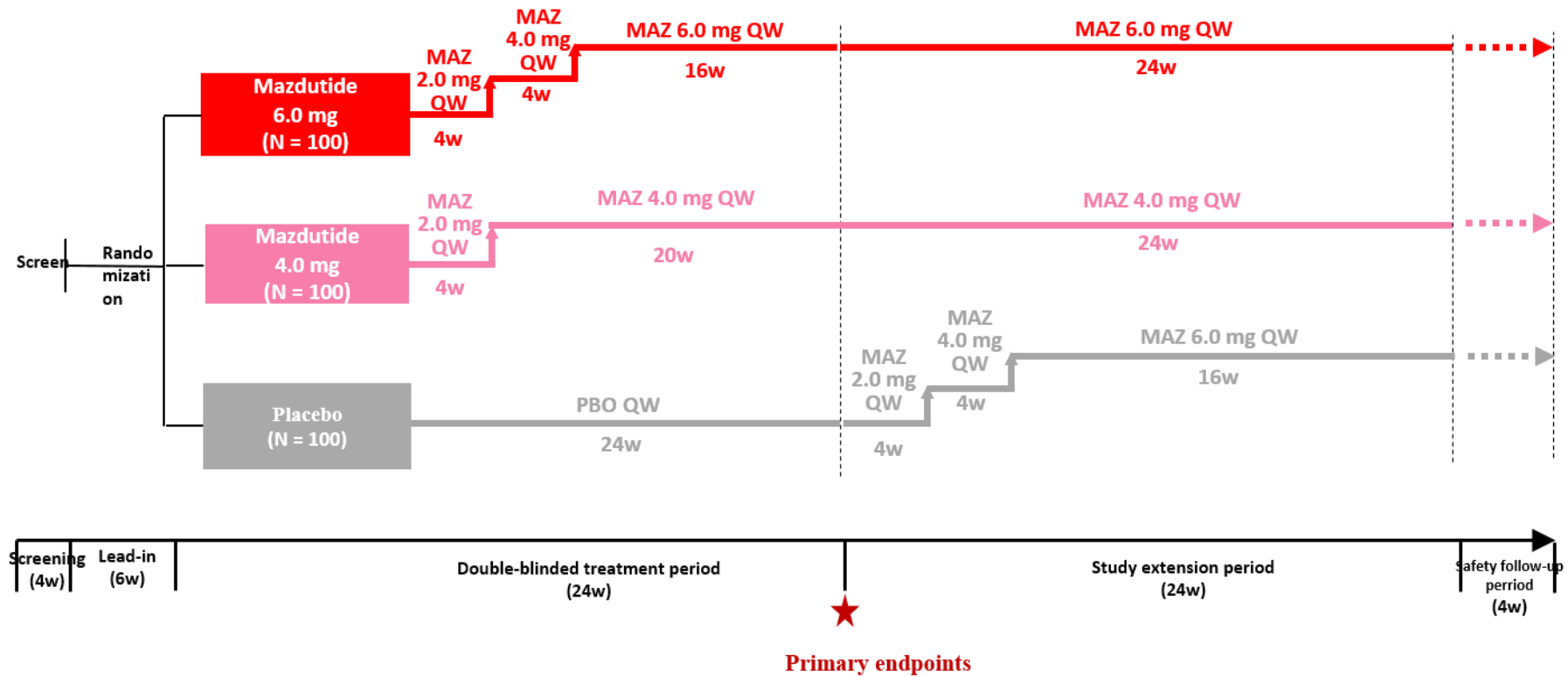


Figure 1. Schematic diagram of the study design

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Abbreviations and Definitions

Abbreviations	Definition in English	Definition in Chinese
AE	Adverse Event	Adverse event
AESI	Adverse event of special interest	Adverse event of special interest
ALB	Albumin	Albumin
ALP	Alkaline phosphatase	Alkaline Phosphatase
ALT	Alanine aminotransferase	alanine aminotransferase
ANC	Absolute Neutrophil Count	Absolute neutrophil count
APTT	Activated Partial Thromboplastin Time	Partial Thromboplastin Time
AST	Aspartate aminotransferase	Aspartate aminotransferase
β-HCG	β human chorionic gonadotropin	human chorionic gonadotropin
CEC	clinical events committee	Clinical Event Committee
CRA	Clinical Research Associate	Clinical Research Associate
CRO	Contract Research Organization	Contract Research Organization
CT	Computed Tomography	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events	Common Terminology Criteria for Adverse Events
EC	Ethics Committee	Ethics Committee
eCRF	Electronic case report form	Electronic case report form
EDC	Electronic Data Capture	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor	Epidermal growth factor receptor
FAS	Full Analysis Set	Full analysis set
FSG	Fasting Serum Glucose	Fasting serum glucose
FT3	Free Triiodothyronine	Free triiodothyronine
FT4	Free Thyroxine	Free thyroxine
GCP	Good Clinical Practice	Good Clinical Practice
γ-GT	γ-glutamyl transferase	γ-glutamyltranspeptidase
HBcAb	Hepatitis B core Antibody	Hepatitis B Core Antibody
HBcAb	Hepatitis B e Antibody	Hepatitis B e antibody
HBcAg	Hepatitis B e Antigen	Hepatitis B e antigen
HBsAb	Hepatitis B surface Antibody	Hepatitis B Surface Antibody
HBsAg	Hepatitis B surface antigen	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus	Hepatitis B virus
HCV	Hepatitis C Virus	Hepatitis C virus
HIV	Human Immunodeficiency Virus	Human immunodeficiency virus
HGB	Hemoglobin	Hemoglobin content

Abbreviations	Definition in English	Definition in Chinese
ICF	Informed Consent Form	Informed Consent Form
IDF	International Diabetes Federation	International Diabetes Federation
Ig	Immunoglobulin	Immunoglobulins
INR	International Normalized Ratio	International normalized ratio
ITT	Intent Analysis	Intention-to-Treat
MRI	Magnetic Resonance Imaging	Magnetic resonance imaging
NYHA	New York Heart Association	New York Heart Association
OCT	Optical Coherence Tomography	Optical Coherence Tomography
PCSA	Potentially Clinically Significant Abnormality	Potentially Clinically Significant Abnormalities
PD	Pharmacodynamics	Pharmacodynamics
PK	Pharmacokinetics	Pharmacokinetics
PLT	Platelet	Platelet count
PPS	Per-Protocol Set	Per-protocol set
PT	Preferred Term	Preferred Term
PTT	Partial Thromboplastin Time	Partial thromboplastin time
RBC	Red Blood Cell	Red blood cell count
SAE	Serious Adverse Event	Serious Adverse Events
SAP	Statistical Analysis Plan	STATISTICAL ANALYSIS PLAN
SOC	System Organ Class	System Organ Class
SS	Safety Set	Safety analysis set
TBIL	Total bilirubin	Serum total bilirubin
TEAE	Treatment Emergent Adverse Event	Treatment-emergent adverse event
TKI	Tyrosine Kinase Inhibitor	Tyrosine kinase inhibitor
TP	Total Protein	Total Protein
TSH	Thyroid Stimulating Hormone	Thyroid Stimulating Hormone
ULN	Upper limit of normal value,	upper limit of normal
UGLU	Urine glucose	Urine Glucose
UPRO	Urine protein	Urine protein
URBC	Urine red blood cell	Urine red blood cells
UREA	Urea	UREA
UWBC	Urinary white blood cell	Urine white blood cells
WBC	White Blood Cell	White blood cell count

1. Introduction

1.1. Study background

Type 2 diabetes (T2D) is a glucose metabolic disorder primarily characterized by chronic hyperglycemia, resulting from insulin resistance and progressive pancreatic β -cell dysfunction^[1]. Poorly controlled hyperglycemia can lead to irreversible microvascular and macrovascular complications, such as vision loss, blindness, renal insufficiency, peripheral neuropathy, myocardial infarction, stroke, and amputation^[2]. According to the global overview of diabetes published by the International Diabetes Federation (IDF) in 2019, the global number of people with diabetes aged 20–79 is about 463 million, and this number is expected to increase to 700 million in 2045. In China, the number of diabetic patients and elderly patients (over 65 years old) with diabetes mellitus ranked first in the world, reaching 116.4 million and 35.5 million, respectively^[3]. Diabetes mellitus, with its high prevalence, insidious onset, and severe complications, represents a grave threat to human health.

Current consensus suggests that the pathogenesis of T2D is primarily attributed to insulin resistance and progressive pancreatic β -cell dysfunction. As the disease progresses, β cells function deteriorates annually, culminating in eventual β -cell failure^[4]. Existing glucose-lowering agents (such as thiazolidinediones, sulfonylureas, and insulin) mainly target improving insulin sensitivity or compensating for secretion defects in β -cell. However, these therapies fail to fundamentally halt β -cell function decline, and are associated with adverse effects such as hypoglycemia and weight gain. Although exogenous insulin administration allows transient pancreatic β -cells rest and indirectly protection, it cannot reverse the progression of β -cell failure^[5].

Glucagon-like peptide-1 receptor (GLP-1R) agonists are promising novel antihyperglycemic agents for T2D patients. GLP-1 is a polypeptide hormone secreted by intestinal L-cells postprandially to exert pleiotropic metabolic effects, such as inhibiting pancreatic β -cell apoptosis and glucagon secretion, promoting pancreatic β -cell proliferation and glucose-dependent insulin synthesis and secretion, enhancing glucose utilization in peripheral tissues, as well as reducing hepatic glucose output^[6]. Endogenous GLP-1 is cleaved and inactivated in plasma by enzymes such as dipeptidyl peptidase-4 (DPP-4) and cleared by rapid glomerular filtration, resulting in an extremely short half-life. GLP-1R agonists address the limitations of native GLP-1 through distinct pharmacological strategies, demonstrating dual effects in glycemic control and body weight reduction for T2D patients, with a significantly lower risk of hypoglycemia compared to conventional therapies. Short-acting GLP-1R agonists (such as exenatide and lixisenatide) and long-acting GLP-1R agonists (such as liraglutide, liraglutide, dulaglutide and semaglutide) commonly used in clinical practice have shown good efficacy and safety in terms of blood glucose control, weight reduction, improvement in blood lipid profile, and cardiovascular outcomes^[7].

Recent years have witnessed the emergence of multi-receptor agonists targeting parallel metabolic pathways as a pivotal focus in metabolic disorder therapeutics. Accumulating preclinical and clinical studies have shown that co-administration of GLP-1R agonists with complementary incretin hormones (e.g., GIP, glucagon) elicits synergistic therapeutic effects, potentiating metabolic benefits beyond monotherapy outcomes^[8]. Importantly, unimolecular multi-receptor agonists with balanced activity profiles across targeted receptors demonstrate superior therapeutic potential compared to single-target agonist monotherapy or combination regimens, which are projected to achieve maximized efficacy, reduced side effect reduction and optimized pharmacokinetics^[9]. A few GLP-1-based single-molecule multiple receptor agonists are in preclinical and clinical development and have shown such synergistic benefits alongside with improved tolerability and improved safety profile. Among them, the dual GLP-1R/glucagon receptor (GCGR) agonist MEDI0382 (AstraZeneca) and the dual GLP-1R/glucose-dependent insulinotropic peptide receptor (GIPR) agonist tirzepatide (Eli Lilly) both exhibited encouraging effects in glycemic control and weight reduction in T2D patients^[10,11].

1.1.1. Study Drug

IBI362 is a long-acting synthetic peptide analogue of mammalian oxyntomodulin (OXM). OXM is a peptide hormone secreted by human intestinal L-cells in response to nutritional intake, exhibiting dual activation of GLP-1R and GCGR. Dual GLP-1R and GCGR agonists synergistically integrate glucagon-driven thermogenesis and lipolysis with GLP-1-mediated gastric emptying delay to achieve substantial weight reduction, while counterbalancing glucagon's hyperglycemic effects through GLP-1's insulinotropic action, thereby enabling coordinated glycemic control^[13,14]. As an engineered OXM analogue, IBI362 is believed to mediate its therapeutic effects through concurrent activation of GLP-1R and GCGR agonism. The molecule achieves extended pharmacokinetic duration via site-specific conjugation of a fatty acyl side chain, enabling sustained therapeutic coverage with once-weekly (QW) subcutaneous administration.

1.1.2. Preclinical results of IBI362

Nonclinical pharmacology data suggested that IBI362 had good binding to GCGR and GLP-1R in mice and monkeys. IBI362 is a full agonist that induces the production of cyclic adenosine monophosphate (cAMP) in cell lines overexpressing the corresponding receptors and in cell lines expressing the corresponding receptors at endogenous levels. In two disease models (diet-induced obese [DIO] mice and streptozocin-induced diabetic [STZ] mice), a significant decrease in blood glucose was observed after repeated administration.

Non-clinical pharmacokinetics evaluations demonstrated that the exposure of IBI362 increased with dose escalation following single and repeated administration in

mice, rabbits, and monkeys, with limited accumulation observed after repeated doses. No significant toxicities of IBI362 were identified in 1-, 6-, and 9-month toxicity, sensitization, and genotoxicity studies in animals. Reproductive toxicity studies established a no observed adverse effect level (NOAEL) of 0.05 mg/kg in both mice fertility and rabbit embryofetal development models. The carcinogenicity evaluation is ongoing. More non-clinical studies are detailed in the IBI362 investigator's brochure.

1.1.3. Clinical study results of IBI362

As of April 28, 2022, Sponsor had conducted and completed a phase 1b study (CIBI362A101) in the Chinese population with T2D and a phase 2 study (CIBI362A201) to evaluate the primary endpoint.

The trial **CIBI362A101** evaluated the safety, tolerability, and pharmacokinetics/pharmacodynamics of multiple injections of IBI362 in Chinese T2D adults. The trial conducted a multicenter, randomized, double-blind, placebo-controlled design. The study drugs IBI362 and placebo were blinded to Investigators and participants, and dulaglutide was set up as an open-label active-controlled group. The results showed that, after 12 weeks of continuous IBI362 treatment, participants showed a significant decrease in glycosylated hemoglobin A_{1c} (HbA_{1c}) levels, with cocurrent decrease in body weight, waist circumference, and body-mass index (BMI). Upon the safety results, IBI362 was well tolerated and safe. The most frequently reported treatment-emergent adverse events (TEAEs) are gastrointestinal AEs. No dose modification of the study drug, severe TEAE, and severe hypoglycemic events were reported throughout the study.

CIBI362A201 is a multi-center, randomized, double-blind, placebo-controlled phase 2 clinical trial to evaluate the efficacy and safety of IBI362 versus placebo and dulaglutide in Chinese T2D patients, and dulaglutide was set up as an open-label active-control group.

Participants were randomized into 5 treatment groups in a 1:1:1:1:1 ratio. The groups are as follows:

- **IBI362 3.0 mg group:** IBI362 1.5 mg for 4 consecutive weeks + IBI362 3.0 mg for 16 consecutive weeks.
- **IBI362 4.5 mg group:** IBI362 1.5 mg for 4 consecutive weeks + IBI362 3.0 mg for 4 consecutive weeks + 4.5 mg for 12 consecutive weeks.
- **IBI362 6.0 mg group:** IBI362 2.0 mg for 4 consecutive weeks + IBI362 4.0 mg for 4 consecutive weeks + 6.0 mg for 12 consecutive weeks.
- **Placebo group:** The number of placebo vials is consistent with that of the IBI362 group, administered for 20 consecutive weeks.
- **Dulaglutide group:** Dulaglutide 1.5 mg, administered for 20 consecutive weeks.

The efficacy and safety results are as follows:

All IBI362 doses demonstrated good hypoglycemic effect in Chinese T2D participants (Figure 2). At week 21, the least squares mean changes in HbA_{1c} from baseline in the IBI362 3.0 mg, IBI362 4.5 mg, IBI362 6.0 mg, dulaglutide 1.5 mg, and placebo groups were -1.4126%, -1.6736%, -1.5407%, -1.3480%, and 0.0283%, respectively. Compared with the placebo group, the estimated differences in the changes in HbA_{1c} from baseline at week 21 in the IBI362 3.0 mg, IBI362 4.5 mg, and IBI362 6.0 mg groups were -1.44% (95% CI: -1.84, -1.04), -1.70% (-2.10, -1.31), and -1.57% (-1.97, -1.17), respectively (All p values <0.0001).

All IBI362 doses demonstrated varying degrees of body weight reduction from baseline (Figure 3). At week 21, the least-squares means change (absolute/percentage) in body weight from baseline in the IBI362 3.0 mg, IBI362 4.5 mg, IBI362 6.0 mg, dulaglutide 1.5 mg, and placebo groups were -3.0206 kg (-4.1249%), -3.8145 kg (-5.3066%), -5.3132 kg (-7.1429%), -1.8247 kg (-2.6946%), and -0.9670 kg (-1.3831%), respectively. Compared with the placebo group, the estimated between-treatment differences in the percent change in body weight from baseline at week 21 in the IBI362 3.0 mg, IBI362 4.5 mg, and IBI362 6.0 mg groups were -2.74% (95% CI: -4.63, -0.86) (p = 0.0045), -3.92% (-5.79, -2.06) (p <0.0001), and -5.76% (-7.65, -3.87) (p <0.0001), respectively.

The proportions of participants achieving HbA_{1c} <7.0% and body weight reduction ≥5% from baseline at week 21 in IBI362 3.0 mg, IBI362 4.5 mg, IBI362 6.0 mg, dulaglutide 1.5 mg, and placebo groups were 18.6%, 32.6%, 52.2%, 14%, and 0%, respectively. At week 21, fasting plasma glucose (FPG) in each IBI362 dose group decreased to varying degrees from baseline.

IBI362 not only showed good hypoglycemic and weight reduction effects, but also effectively reduced waist circumference, blood pressure, blood lipids, and liver enzymes, bringing multiple metabolic benefits to T2D patients.

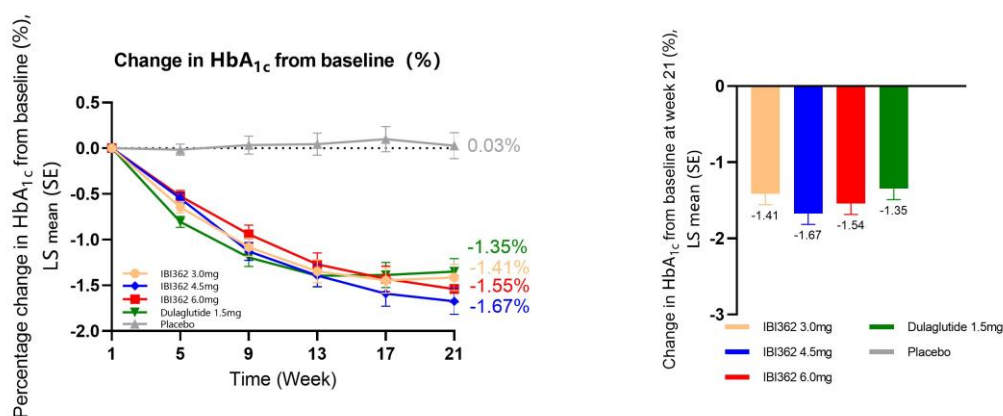


Figure 2. Primary efficacy endpoint in CIBI362A201 — HbA_{1c}

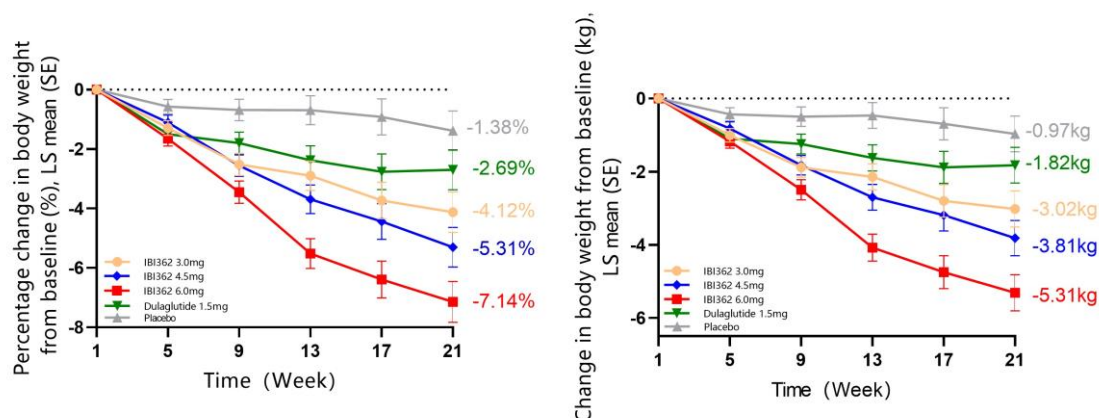


Figure 3. Secondary efficacy endpoints in CIBI362A201 — Body weight

Upon the safety outcomes, IBI362 was safe and well tolerated. The overall safety profile was consistent with that of the Phase 1b study, with no new safety signals identified, and was in line with other GLP-1R agonists. TEAEs were mostly mild or moderate in severity. Serious adverse events (SAEs) occurred in 11 participants, among which all SAEs in the IBI362 groups were judged by Investigators to be unrelated to the study drug. No severe hypoglycemic events and no acute pancreatitis reported (Table 2). The most commonly reported TEAEs (incidence >10%) included nausea, vomiting, diarrhea, and decreased appetite, most of which were mild or moderate. The AEs in the study were basically consistent with same-class drugs and no unexpected AEs were reported^[15].

Cardiovascular AEs occurring in the study were predominantly mild in severity, with incidence rate showing no dose-dependent trend across treatment groups. The most common cardiovascular adverse events were supraventricular extrasystoles, palpitations, sinus tachycardia, ventricular extrasystoles. The incidence of hypoglycemic events in the IBI362 3.0 mg, IBI362 4.5 mg, IBI362 6.0 mg, dulaglutide 1.5 mg, and placebo groups was 3.9%, 8.2%, 14.3%, 2.0%, and 7.8%, respectively. Most of the hypoglycemic events were asymptomatic hypoglycemia and probable symptomatic hypoglycemia, with no severe hypoglycemic event reported.

Table 2. Safety results in CIBI362A201 - Treatment-emergent adverse events

n (%)	IBI362 3.0 mg (n=51)	IBI362 4.5 mg (n=49)	IBI362 6.0 mg (n=49)	Dulaglutide 1.5mg (n=50)	Placebo (n=51)
Treatment-emergent AE (TEAE)	43(84.3%)	37(75.5%)	39(79.6%)	38(76.0%)	33(64.7%)
Treatment-related TEAE	34(66.7%)	32(65.3%)	30(61.2%)	24(48.0%)	12(23.5%)
Serious TEAE	0	1(2.0%)	1(2.0%)	1(2.0%)	1(2.0%)
Serious TRAE	0	1(2.0%)	1(2.0%)	0	0
TEAE leading to treatment discontinuation	0	0	0	1(2.0%)	0
TRAE leading to treatment discontinuation	0	0	0	0	0
Serious AE (SAE)	0	0	3(6.1%)	4(8.0%)	4(7.8%)
Treatment-related SAE	0	0	0	2(4.0%)	0
Hypoglycemic event	2(3.9%)	4(8.2%)	7(14.3%)	1(2.0%)	4(7.8%)
Serious hypoglycemic event**	0	0	0	0	0
Acute Pancreatitis	0	0	0	0	0
Most common TEAE (PT) (incidence >10%)					
Nausea	11(21.6%)	12(24.5%)	12(24.5%)	15(30.0%)	3(5.9%)
Vomiting	6(11.8%)	7(14.3%)	8(16.3%)	7(14.0%)	1(2.0%)
Diarrhea	19(37.3%)	20(40.8%)	14(28.6%)	8(16.0%)	4(7.8%)
Loss of appetite	15(29.4%)	13(26.5%)	15(30.6%)	9(18.0%)	4(7.8%)

*HLT: all hypoglycemic events (no classification); **LLT: Severe hypoglycemic event; PT: pancreatitis

1.2. Risk/benefit assessment

1.2.1. Potential risks

Safety data from completed IBI362 clinical trials indicated that the most frequently reported TEAEs were gastrointestinal-related, predominantly including decreased appetite, hiccups, nausea, vomiting, dyspepsia, abdominal distension, diarrhea, and constipation. Consistent with the established safety profile of GLP-1R agonists, the majority of adverse reactions observed in these trials were gastrointestinal. Investigators were advised to pay special attention in clinical studies and give corresponding symptomatic treatment when necessary to reduce the risk of drug use in participants. Meanwhile, attention should be paid to excluding participants with potential related risks

in the screening period of clinical trials to avoid exacerbation of the original disease caused by drug stimulation. In addition, according to the results of previous clinical studies of GLP-1 drugs and IBI362, the treatment with IBI362 may increase the heart rate, and AEs such as sinus tachycardia may occur during the study. Therefore, cardiovascular AEs that occur during the study should be closely monitored.

1.2.2. Potential benefits

The results of the completed CIBI362A201 study showed that IBI362 was well tolerated and safe in Chinese T2D participants following a 20-week continuous treatment. All IBI362 doses showed significant hypoglycemic efficacy in T2D participants with HbA_{1c} decrease of 1.41%–1.67% from baseline at week 21, compared to 1.35% with dulaglutide. Concurrently, all IBI362 dose groups demonstrated significant weight reduction efficacy, with body weight reduction of 4.12%–7.14% from baseline at week 21 versus 2.69% with dulaglutide. At week 21, the proportion of participants with HbA_{1c} <7% and weight reduction ≥5% was 18.6%–52.2% across the IBI362 dose groups and 14% in the dulaglutide group. In addition to hypoglycemic and weight-reduction effects, varying degrees of improvements in blood pressure, blood lipid levels, and liver enzyme levels were also observed in each IBI362 dose group. Based on the above results, it is expected that the development of IBI362 can bring comprehensive benefits to Chinese T2D patients.

2. Study Objectives, Endpoints, and Estimands

2.1. Study objectives and endpoints

Study Objectives	Study Endpoints
Primary objective	Primary endpoint
To validate that the change from baseline in HbA_{1c} level at week 24 in the IBI362 group is superior to that in the placebo group.	Change from baseline in HbA_{1c} at week 24.
Key secondary objectives	Key secondary endpoints
To validate that the efficacy of glycemic control and weight reduction in the IBI362 group at week 24 is superior to that in the placebo group.	- At week 24: - Proportion of participants achieving HbA_{1c} <7.0%; - Proportion of participants achieving HbA_{1c} <7.0% and weight reduction ≥5% from baseline. - Proportion of participants achieving weight reduction ≥5% from baseline;

	– Percent change from baseline in body weight.
Other secondary objectives	Other secondary endpoints
• To evaluate the effects of IBI362 in cardiovascular and metabolic parameters; • To assess patient-reported outcomes (PROs); • To evaluate the safety and tolerability of IBI362; • To evaluate the pharmacokinetics (PK) of IBI362.	<u>Efficacy endpoints:</u> • At week 48: – Change in HbA_{1c} from baseline; – Proportion of participants achieving HbA_{1c} < 7.0%; – Proportion of participants achieving weight reduction ≥5% from baseline; – Proportion of participants achieving HbA_{1c} <7.0% and weight reduction ≥ 5%; – Percent change from baseline in body weight. • At weeks 24 and 48: – Proportion of participants achieving HbA_{1c} ≤6.5% and HbA_{1c} <5.7%; – Changes in FPG from baseline; – Change in serum 1,5-anhydroglucitol (1,5-AG) from baseline; – Change in 7-point fingertip blood glucose from baseline; – Change in waist circumference and BMI from baseline; – Absolute change in body weight from baseline; – Proportion of participants achieving ≥10% weight reduction from baseline; – Change in systolic and diastolic blood pressure from baseline; – Blood lipid [total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels from baseline; – Change in blood uric acid (UA) level from baseline; – Changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels from baseline; – Change in urine albumin-to-creatinine ratio

	from baseline; – Change in patient-reported outcome (PRO) questionnaire scores from baseline: Diabetes Treatment Satisfaction Questionnaire (DTSQ) score; european Quality of Life-5 Dimensions (EQ-5D-5L); – Changes in HOMA2-B and HOMA2-IR from baseline. <u>Safety endpoints:</u> • The incidence and severity of adverse events (AEs) and their correlation with the study drug. • Changes in vital signs, physical examinations, laboratory tests, and electrocardiograms (ECG) , as well as the incidence of abnormal parameters from baseline. • To evaluate the immunogenicity of IBI362. <u>Pharmacokinetic and pharmacodynamic endpoints:</u> • To evaluate the population PK characteristics of IBI362, including but not limited to: time to maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), area under curve (AUC), volume distribution (V), half-life ($T_{1/2}$), and clearance (CL). • To assess the changes in PD parameters (fasting insulin and fasting C-peptide) at different time points before and after administration.
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2.2. Estimands

2.2.1. Treatment-policy estimand

- **Clinical issues of interest:** Glycemic control efficacy of IBI362 (treatment regimens of the 4.0 mg and 6.0 mg groups) in Chinese T2D adults with inadequate control by diet and exercise alone, regardless of whether the participants complete the entire treatment with IBI362 in compliance with the protocol.
- **Population:** T2D adults who meet the inclusion/exclusion criteria, have been successfully lead-in and have inadequately controlled diet and exercise with at least one dose of the study drug.
- **Treatments:**

- IBI362 4.0 mg dose group: Subcutaneous injection once weekly (QW); the starting dose was IBI362 2.0 mg, and after 4 weeks of continuous administration, the dose was increased to IBI362 4.0 mg, and the administration lasted for 44 weeks.
- IBI362 6.0 mg dose group: Subcutaneous injection QW; the starting dose was IBI362 2.0 mg. After 4 weeks of continuous administration, the dose was increased to IBI362 4.0 mg. After 4 weeks of continuous administration, the dose was further increased to IBI362 6.0 mg for 40 weeks.
- Placebo group: Subcutaneous injection QW for 24 consecutive weeks during the double-blind period, followed by switching to IBI362 2.0 mg QW. After 4 weeks of consecutive administration, the dose was increased to 4.0 mg, and then to 6.0 mg QW for 4 consecutive weeks for 16 weeks.
- **Endpoints:** Primary and secondary efficacy endpoints.
- **Intercurrent events and handling strategies:**

Intercurrent event	Handling strategy	Remarks
Premature discontinuation of treatment and use of rescue therapy for any cause	Treatment-policy strategy: Data after intercurrent events will continue to be used.	This management strategy reflects real-world use of the study drug, and the use of the treatment-policy strategy allows for assessment of efficacy across drug class use scenarios.

- **Population-level summary:** The efficacy endpoints will be summarized for both the IBI362 4.0 mg and 6.0 mg treatment groups after 24 and 48 weeks of continuous dosing. Additionally, the efficacy of the IBI362 4.0 mg and 6.0 mg groups will be compared with that of the placebo group after 24 weeks of continuous dosing during the double-blind treatment period.

2.2.2. Efficacy estimands

- **Clinical issues of interest:** Glycemic control efficacy of IBI362 (treatment regimens of the 4.0 mg and 6.0 mg groups) in Chinese T2D adults with inadequate control by diet and exercise alone, if the participants complete the entire treatment with IBI362 in compliance with the protocol.
- **Population:** T2D adults who meet the eligibility criteria, are successfully enrolled, randomized, and have inadequate glycemic control after diet and exercise alone with at least one dose of the study drug.
- **Treatments:**

- IBI362 4.0 mg dose group: Subcutaneous injection QW; the starting dose was IBI362 2.0 mg, and after 4 weeks of continuous administration, the dose was increased to IBI362 4.0 mg, and the administration lasted for 44 weeks.
 - IBI362 6.0 mg dose group: Subcutaneous injection QW; the starting dose was IBI362 2.0 mg. After 4 weeks of continuous administration, the dose was increased to IBI362 4.0 mg. After 4 weeks of continuous administration, the dose was further increased to IBI362 6.0 mg for 40 weeks.
 - Placebo group: Subcutaneous injection QW for 24 consecutive weeks during the double-blind period, followed by switching to IBI362 2.0 mg QW. After 4 weeks of consecutive administration, the dose was increased to 4.0 mg, and then to 6.0 mg QW for 4 consecutive weeks for 16 weeks.
- **Endpoints:** Primary efficacy endpoint and key secondary efficacy endpoints.
 - **Intercurrent events and handling strategies:**

Intercurrent event	Handling strategy	Remarks
Premature discontinuation of treatment and use of rescue therapy for any cause	Hypothetical strategy: The efficacy data observed after the occurrence of the intercurrent event will no longer be used, and the efficacy data after the intercurrent event will be imputed using appropriate statistical analysis methods under the assumption that the participant has not experienced the intercurrent event.	This management strategy reflects the efficacy of the study drug under ideal conditions. The use of a hypothetical strategy eliminates the possibility of confounding effects of nonstudy drugs being confounded by both rescue therapy and other therapies administered after premature treatment discontinuation.

- **Population-level summary:** The efficacy endpoints will be summarized and the efficacy of the IBI362 4.0 mg and 6.0 mg groups will be compared with that of the placebo group after 24 weeks of consecutive administration during the double-blind treatment period.

3. Study Design

3.1. Overall design

This is a multi-center, randomized, double-blind, placebo-controlled phase 3 trial evaluating the efficacy and safety of IBI362 in type 2 diabetes (T2D) adults with inadequately controlled diet and exercise alone. This trial aims to enroll approximately

300 T2D participants who do not reach the target HbA1c after at least 2 months of diet and exercise alone. Participants are required to maintain control of diet and exercise throughout the study.

The entire study period includes a 4-week screening period, a 6-week lead-in period, a 24-week double-blind treatment period, a 24-week study extension period, and a 4-week safety follow-up period.

Screening period:

Relevant examinations were performed to check the inclusion and exclusion criteria and determine the eligibility of the participants.

Lead-in period:

Eligible participants will enter the lead-in period, during which anyone using hypoglycemic medication before randomization is ineligible and withdraw from the trial.

During the lead-in period, participants will be trained on disease monitoring [e.g., self-monitoring of blood glucose (SMBG)], disease management procedures, study diary cards, and study procedures. Participants should return to the hospital within the last week of the lead-in period for retesting of HbA1c, FPG or FSG, body weight, etc., and assessment of randomization criteria.

Double-blind treatment period:

Participants who met the randomization criteria were randomized into IBI362 4.0 mg group, IBI362 6.0 mg group, or placebo group in a 1:1:1 ratio. The randomization stratification factors were HbA1c <8.5% or HbA1c $\geq$ 8.5% prior to randomization (V3). During the double-blind treatment period, IBI362 and placebo will be blinded to Investigator, participants, and Sponsor. The dosing regimens are as follows:

- **IBI362 4.0 mg group:** Subcutaneous injection once weekly (QW); the starting dose was IBI362 2.0 mg, and after 4 weeks of consecutive administration, the dose was increased to IBI362 4.0 mg, and the administration lasted for 20 weeks.
- **IBI362 6.0 mg group:** Subcutaneous injection QW; the starting dose was IBI362 2.0 mg. After 4 weeks of consecutive administration, the dose was increased to IBI362 4.0 mg. After 4 weeks of consecutive administration, the dose was further increased to IBI362 6.0 mg for 16 weeks.
- **Placebo group:** Subcutaneous injection QW for 24 consecutive weeks.

Study extension period:

After completing the double-blind treatment period, the participants will be transitioned to the extension period of the study with the following dosing regimens:

- **IBI362 4.0 mg group:** Subcutaneous injection QW; IBI362 4.0 mg, consecutive administration for 24 weeks.
- **IBI362 6.0 mg group:** Subcutaneous injection QW; IBI362 6.0 mg, consecutive administration for 24 weeks.
- **Placebo group:** Switching to IBI362 treatment with the starting dose of IBI362 2.0 mg. After 4 weeks of consecutive administration, the dose was adjusted to IBI362 4.0 mg. After 4 weeks of consecutive administration, the dose was increased to IBI362 6.0 mg for 16 weeks.

Safety follow-up period:

During the safety follow-up period, Investigator can decide the hypoglycemic regimen for participants at his/her discretion (GLP-1 receptor agonists and DPP4 inhibitors are prohibited).

3.2. Dose modification

Dose modifications in the double-blind treatment period and the extension period of the study:

Dose resumption after dose reduction is not allowed.

Management of gastrointestinal adverse events:

During the treatment period, if Investigator assesses that the participant is still intolerant to gastrointestinal adverse events after dietary pattern adjustment or symptomatic treatment, dose interruption may be considered:

- Up to one less dose is allowed every 4 weeks;
- If a participant's gastrointestinal AEs resolve after dose interruption, Investigator should resume the dose before dose interruption, or initiate the next dose level at investigator's discretion according to the participant's condition; the total treatment period remains 48 weeks.

If a participant is still unable to tolerate gastrointestinal AEs despite the above measures, Investigator may discuss with Sponsor and decide to increase the frequency of dose interruptions or discontinue the treatment.

Participants should communicate with Investigator before deciding whether to interrupt the study drug. Participants who may require re-titration from the starting dose should go to the hospital and receive the study drug after discussion with Sponsor based on Investigator's assessment.

3.3. Study design rationale

3.3.1. Rationale for dose selection

A phase 3 clinical study of IBI362 is intended to be conducted in Chinese T2D adults,

with a dosing regimen of 2 mg QW $\times$ 4 + 4 mg QW $\times$ for maintenance and 2 mg QW $\times$ 4 + 4 mg QW $\times$ 4 + 6 mg QW $\times$ for maintenance. This dose and dosing regimen were selected based on the results of phase 1b (CIBI362A101) and phase 2 (CIBI362A201) studies of IBI362 in T2D adults.

The safety and efficacy of two dosing regimens, 1.5 mg QW $\times$ 4 + 3.0 mg QW $\times$ 4 + 4.5 mg QW $\times$ 4 and 2 mg QW $\times$ 4 + 4 mg QW $\times$ 4 + 6 mg QW $\times$ 4, have been validated in the trial CIBI362A101. IBI362 showed favorable safety profile in the above two dose groups. The most common TEAEs were gastrointestinal. During the study, there was no dose modification of the study drug, no severe treatment-emergent adverse event, and no severe hypoglycemic event. At the same time, it has shown good hypoglycemic and weight-reduction effects. In addition, varying degrees of improvements in blood pressure, blood lipid levels, and transaminase levels of participants receiving IBI362 were also observed in the trial.

The efficacy and safety of 1.5 mg QW $\times$ 4 + 3.0 mg QW $\times$ 4 + 4.5 mg QW $\times$ for maintenance and 2 mg QW $\times$ 4 + 4 mg QW $\times$ 4 + 6 mg QW $\times$ for maintenance were validated again in CIBI362A201. IBI362 showed favorable safety profile in the above two dosing regimens. The most common TEAEs were gastrointestinal. No significant dose-dependent gastrointestinal reactions were observed. No significant increase in the incidence of AEs at the low dose of 6 mg in the high-dose group. The overall safety of IBI362 was comparable to or slightly better than that of other marketed peer agents. The overall safety profile was completely controllable. In terms of hypoglycemic efficacy, HbA_{1c} in both IBI362 4.5 mg and 6 mg groups decreased significantly from baseline. Although the results were similar, other hypoglycemic efficacy endpoints (changes in FPG from baseline and HbA_{1c} achievement rate) showed a dose-dependent effect. Upon the efficacy in weight reduction, IBI362 3 mg, 4.5 mg, and 6 mg groups showed significant dose-dependent weight reduction effects, and it was also observed that medium- and high-dose groups could better improve metabolic parameters (blood pressure, blood lipids, and liver enzymes).

Higher doses have better overall benefits under safe and controllable conditions, and can provide a more personalized treatment regimen and treatment options for diabetic patients. On the premise of considering the comprehensive benefits of diabetic patients, combined with the efficacy and safety data of previous studies of IBI362, it is supported to carry out the phase 3 study with two dosing regimens: 2 mg QW $\times$ 4 + 4 mg QW $\times$ for maintenance therapy and 2 mg QW $\times$ 4 + 4 mg QW $\times$ 4 + 6 mg QW $\times$ for maintenance therapy.

3.3.2. Rationale for the primary endpoint selection

The primary endpoint selection was in accordance with the relevant provisions regarding efficacy evaluation criteria outlined in the Guidance for Industry on Diabetes

Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention issued by U.S. Food and Drug Administration (FDA) and the Guidelines for Clinical Trials of Drugs and Biological Products for the Treatment of Diabetes issued by China's National Medical Products Administration (NMPA).

3.4. Clinical event committee

Sponsor will establish a clinical events committee (CEC). The CEC, which was composed of independent clinical experts, will review investigator-reported major cardiovascular events at each trial site to determine whether the events met the protocol-specified criteria. This process remains independent from Sponsor and its representatives to ensure unbiased assessments. Specific procedures and definitions are outlined in the CEC charter.

3.5. Definition of end of study

A participant is considered to have completed the study if he/she has completed the safety follow-up (Week 52).

The end of study for an individual participant is defined as the completion of the study or premature withdrawal from the study.

The end of the study is considered as the last visit for the last participant.

3.6. Clinical criteria for study discontinuation/early termination

This study may be temporarily suspended or prematurely terminated if sufficient justifiable reasons arise. The party suspending or terminating the study shall provide written notice to participants, investigators, funding agencies, and regulatory authorities, with documentation of the reasons for suspension/termination. In the event of premature termination or suspension, the Principal Investigator shall promptly notify participants and the Ethics Committee (EC), providing rationale for the action. Where applicable, investigators will contact participants to communicate changes in scheduled visit timelines.

Circumstances that may require termination or suspension include but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- The efficacy rationale should be termination/suspension of the study;
- Inability to meet protocol compliance requirements;
- Incomplete and/or insufficient data for evaluation;
- Determination that the primary endpoint has been met;
- Plans to change or stop the development of the study drug.

The study may continue only if issues related to safety, protocol compliance, and data quality are addressed, and the requirements of the EC and/or NMPA are met.

If Sponsor decides to discontinue the supply of the study drug, sufficient advance notice will be provided to allow for appropriate adjustments to the participant's treatment.

4. Study Population

Deviations from the eligibility criteria will not be allowed as they could have impacted the scientific integrity, regulatory acceptability, and/or participant safety of the study. Therefore, participants must meet protocol-specified eligibility criteria.

4.1. Inclusion criteria

Participants must meet **all** of the following inclusion criteria to be included in the study:

1. Diagnosis of T2D for at least 2 months according to the 1999 WHO criteria (see [Appendix 6](#)).
2. Aged ≥ 18 years at the time of signing the informed consent form (ICF).
3. Participants with inadequate glycemic control after diet and exercise alone within 2 months prior to screening, with $7.5\% \leq \text{HbA}_{1c} \leq 10.5\%$ tested at a local laboratory at screening.
4. BMI ≥ 23 kg/m² at screening.
5. Able to maintain a stable diet and exercise lifestyle during the study.
6. Participants who voluntarily sign the ICF and agree to strictly follow the requirements of this protocol.

4.2. Exclusion criteria

Participants meeting **any** of the following exclusion criteria must be excluded from this study:

1. Participants who, judged by Investigator, may be allergic to components of the study drug or similar drugs.
2. Body weight change $>5\%$ (complaint) within 12 weeks prior to screening.
3. Use of any of the following medications or therapies prior to screening:
 - 1) Have used any hypoglycemic drug within 2 months prior to screening; have used ≥ 3 hypoglycemic drugs in combination more than 2 months prior to screening.
 - 2) Use of GLP-1R agonist or GLP-1R/GCGR agonist or GIPR/GLP-1R agonist or GIPR/GLP-1R/GCGR agonist within 2 months prior to screening; participants who have discontinued the above drugs due to lack of efficacy or intolerance more than 2 months prior to screening are also excluded.

- 3) Use of insulin for diabetes control within 3 months prior to screening, except for short-term (cumulative use ≤ 14 days) use of insulin in an acute state, such as acute illness, hospitalization, or elective surgery. Last treatment with insulin was < 14 days from screening day in any case.
 - 4) Use of drugs with weight loss efficacy within 2 months prior to screening or planned use during the trial, such as semaglutide, beinaglutide, liraglutide, orlistat, sibutramine hydrochloride, phenylpropanolamine, chlorphenazone, phentermine, lorcaserin hydrochloride, phentermine, phentermine/topiramate, diethylpropion, and naltrexone/bupropion.
 - 5) Use of Chinese herbal medicines, other traditional medicines, and health products with hypoglycemic effect within 2 months prior to screening.
 - 6) Currently receiving chronic (> 2 weeks) systemic glucocorticoids or having used glucocorticoids within 4 weeks prior to screening (excluding topical, ophthalmic, intranasal, or inhaled administration).
 - 7) Current use of central nervous system stimulants, excluding beverages containing caffeine, at screening.
 - 8) Have participated in other clinical trials and received study treatment within 3 months prior to screening.
 - 9) History of alcohol and drug abuse at screening. Average weekly alcohol intake: more than 21 units for males and more than 14 units for females (1 unit = 360 mL of beer, or 150 mL of red wine, or 45 mL of distilled spirits/liquor).
4. History or evidence of any one of the following diseases:
- 1) Previously diagnosed with type 1 diabetes mellitus (T1D) [including latent autoimmune diabetes in adults (LADA)].
 - 2) Two or more episodes of ketoacidosis, diabetic hyperosmolar state, or lactic acidosis within 6 months prior to screening.
 - 3) History of severe hypoglycemic episodes within 6 months prior to screening, defined as neuroglycopenic symptoms requiring assistance of another person for recovery, or hypoglycemia unawareness or insufficient awareness of hypoglycemic symptoms. Participants who, judged by Investigator, are unable to communicate and understand symptoms of hypoglycemia and appropriate treatment should also be excluded from this study.
 - 4) History of acute or chronic pancreatitis, or blood amylase or lipase $> 2.0 \times$ upper limit of normal (ULN) or fasting TG ≥ 5.64 mmol/L (500 mg/dL) at screening.
 - 5) History of gastroparesis or bariatric surgery, or abnormal gastric emptying clinically significant judged by Investigator.

- 6) History or presence at screening of proliferative diabetic retinopathy, or diabetic macular edema, or nonproliferative diabetic retinopathy requiring urgent treatment.
- 7) Acute and chronic hepatitis (except chronic hepatitis B), symptoms and signs of other liver diseases, or ALT $>3.0 \times \text{ULN}$ (ALT $>5.0 \times \text{ULN}$ for non-alcoholic fatty liver disease), or AST $>3.0 \times \text{ULN}$, or total bilirubin (TBIL) $>2.0 \times \text{ULN}$.
- 8) History or family history of medullary thyroid cancer, multiple endocrine neoplasia (MEN) 2A or 2B.
- 9) Hyperthyroidism or hypothyroidism confirmed by clinical evaluation and/or abnormal thyroid stimulating hormone (TSH) levels that in Investigator's judgment would increase subject risk; except for participants on stable-dose thyroid hormone replacement therapy for at least 2 months with normal thyroid function currently and expected to maintain consistent dosage throughout the study period.
- 10) A previous definitive diagnosis of autonomic neuropathy manifested by urinary retention, resting tachycardia, orthostatic hypotension, or diabetic diarrhea.
- 11) History of acute myocardial infarction, unstable angina, coronary artery bypass graft, percutaneous coronary intervention (except diagnostic angiography), transient ischemic attack (TIA), cerebrovascular accident, severe arrhythmia (such as ventricular fibrillation, ventricular flutter, atrial fibrillation, atrial flutter, third-degree atrioventricular block, etc.), and pre-excitation syndrome within 6 months prior to screening; or a previous diagnosis of decompensated heart failure or Grade III or IV heart failure identified by the New York Heart Association (NYHA).
- 12) A 12-lead ECG showing heart rate <50 bpm or >100 bpm, or ECG indicative of active cardiac disease, or ECG abnormalities judged by Investigator as potentially interfering with ECG result interpretation during follow-up (with specific exclusion of QTcF >500 ms).
- 13) Poorly controlled hypertension at screening, with systolic blood pressure (SBP) ≥ 160 mmHg or diastolic blood pressure (DBP) ≥ 100 mmHg; or antihypertensive drugs (dose or type of drugs) modified within 30 days before screening; evidence of renal artery stenosis, or labile blood pressure (including postural hypotension, etc.).
- 14) Active or untreated malignant tumors within 5 years prior to screening, or in remission of clinical malignant tumors (except for patients with basal cell carcinoma and squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the prostate, or papillary thyroid carcinoma without

recurrence after surgery).

- 15) Serum calcitonin ≥ 35 ng/L (pg/mL) at screening.
 - 16) Glomerular filtration rate eGFR < 45 mL/min/1.73 m² at screening, estimated using the CKD-EPI formula (see [Appendix 2](#)).
 - 17) History of atopic reactions (clinical manifestations of severe or multiple allergies) or clinically significant history of multiple or severe drug allergies, or intolerance to topical glucocorticoids, or severe post-treatment hypersensitivity reactions (including but not limited to erythema multiforme, linear immunoglobulin A dermatitis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis).
 - 18) History of or evidence of human immunodeficiency virus (HIV) infection, positive HIV antibody, positive hepatitis C virus (HCV) antibody, or positive syphilis antibody at screening.
 - 19) Hepatitis B surface antigen (HBsAg) positive and hepatitis B virus DNA copy number ≥ 1000 IU/mL (drug-naïve participants) or receiving anti-hepatitis B virus (HBV) treatment at screening.
 - 20) History of organ transplantation (except corneal transplantation), or preparing for organ transplantation.
 - 21) Presence of serious active and uncontrolled physical conditions or medical history, which may be in a dangerous state during the use of the study drug or interfere with the interpretation of the efficacy and safety data of this study, as judged by Investigator at screening.
 - 22) History of or presence of psychiatric disorders at screening that, in Investigator's judgment, render the participant unsuitable for participation in this study.
 - 23) Blood donation and/or blood loss of ≥ 450 mL or bone marrow donation, blood transfusion or severe blood loss within 3 months prior to screening, or presence of hemoglobinopathy, hemolytic anemia, sickle cell anemia, or hemoglobin < 110 g/L (males) or < 100 g/L (females) at screening, or presence of any other known factor that could interfere with HbA_{1c} test results.
5. Pregnant or lactating women, or men or women of childbearing potential who are unwilling to use contraception during the entire study period until 8 weeks after the end of the study.
 6. Participants who are not suitable for participating in this study due to any other factors that may affect the efficacy or safety evaluation of this study, as judged by Investigator.

4.3. Randomization Criteria

HbA_{1c}, FPG, or FSG, and body weight should be retested at V3 in the lead-in period, and participants should meet all of the following randomization criteria before randomization:

1. Local laboratory testing $7.0\% \leq \text{HbA}_{1c} \leq 10.5\%$.
2. Local laboratory testing FSG or FPG ≤ 15.0 mmol/L.
3. BMI ≥ 23 kg/m² and weight change of $\leq 5\%$ during the lead-in period (V2 and V3).

4.4. Study restrictions and precautions

4.4.1. Eligibility restrictions for study participation

- Participants should not donate blood during the study and within 8 weeks after the end of the study.
- Participants are not allowed to participate in other clinical trials during the study and within 8 weeks after the end of the study.
- During the study, attention should be paid to diet and exercise control, and overeating is not allowed.
- Average weekly alcohol intake during the study: less than 21 units for males and less than 14 units for females (1 unit = 360 mL of beer, or 150 mL of red wine, or 45 mL of distilled spirits/liquor).

4.4.2. Other restrictions

4.4.2.1 Childbearing age

Women with childbearing potential are defined as those who have had menarche, have not undergone sterilization (i.e., bilateral tubal ligation, bilateral salpingectomy, or hysterectomy), and are not postmenopausal.

For women in childbearing age who are sexually active with male partners who have not undergone sterilization, and men who have not undergone sterilization and are sexually active with women of childbearing age, the participants and their partners must use at least 1 acceptable method of effective contraception listed in [Table 3](#) from screening to 8 weeks after the end of the study, and discuss with a responsible physician about the discontinuation of contraception after this time point. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable contraceptive methods.

Table 3. Effective method of contraception (at least 1 method must be used)

Barrier method	Intrauterine device approach	Hormonal methods
Male condom with spermicide	Copper-T IUD	Implant

Barrier method	Intrauterine device approach	Hormonal methods
Cervical cap with spermicide	Progesterone-T IUD ^a	Hormonal injection
Diaphragm with spermicide	Levonorgestrel-releasing intrauterine system (e.g. Mirena [®]) ^a	Combined pill Low-dose oral contraceptive pill Birth Control Patch

a. Also considered a hormonal method

Menopause is defined as the cessation of menses for 12 months in a woman without an alternative medical cause. The requirements according to age are as follows:

- Females >50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy, and luteinizing hormone and follicle stimulating hormone levels within the postmenopausal range, are considered menopausal.
- Females ≤50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy, radiation-induced ovariectomy and the time from the last menorrhea >1 year, chemotherapy-induced amenorrhea and the time from the last menorrhea >1 year, or surgical sterilization (bilateral ovariectomy or hysterectomy), are considered menopausal.

4.4.2.2 Pregnancy

No any study results on whether IBI362 can penetrate the placental barrier is reported so far, therefore it is not recommended to use during pregnancy. Pregnant women must not be enrolled in this study.

4.4.2.3 Lactation

It is unknown whether IBI362 is secreted in breast milk. Considering that many drugs are present in breast milk, lactating women should not be included in this study.

4.5. Screening of participants

4.5.1. Enrollment procedures

Investigator will enroll participants by the following steps:

1. Obtaining an ICF signed by the participant prior to any study-related procedures.
2. Formally confirming the participants' eligibility by the Principal Investigator or trained designee after reviewing the inclusion/exclusion criteria.

Sponsor will monitor the enrollment of each treatment group to ensure that the sample size of each group meets the study requirements.

Participants who do not meet the relevant criteria of this study (screen failure) may be re-screened. If re-screening of a participant is considered, Investigator must contact

Sponsor's medical monitor. Each participant can be re-screened once. Participants must sign the ICF again and receive a new identification number when they are re-screened. Participants who have failed to enter the lead-in period are not allowed to be re-screened or re-lead-in.

If Investigator believes that the examination/measurement results that do not meet the inclusion/exclusion criteria (including vital signs, BMI, ECG, ophthalmoscopy, and laboratory tests, etc.) are caused by examination/measurement errors or other objective reasons that can be explained (except participantively speculated reasons) and need to be retested, these indicators can only be retested once (must be performed during the screening period), and this situation is not considered re-screening; those who fail the screening because HbA_{1c} does not meet the inclusion criteria cannot be retested or re-screened. If the body weight, FSG, or FPG that do not meet the randomization criteria during the lead-in period are considered by Investigator to be caused by examination/measurement errors or other objective reasons that can be explained (except for participantively speculated reasons) and need to be retested, this parameter can only be retested once (must be performed during the lead-in period), and this situation is not considered as re-screening or re-run; HbA_{1c} that fails to meet the randomization criteria and thus fails the lead-in, cannot be retested.

Participants who withdraw from the study for any reason are not allowed to be re-screened.

4.5.2. Procedures for handling incorrectly enrolled participants

The inclusion criteria must be strictly followed. If an ineligible participant is enrolled, Sponsor's study physician and Investigator must discuss whether to allow the participant to continue participating in the study and whether to use the study drug.

4.6. Treatment discontinuation/withdrawal of participants

4.6.1. Suspension of treatment

After randomization, Investigator may temporarily suspend the administration of the study drug under certain special circumstances, such as the participant experiencing an AE, or the participant being unable to administer the drug due to other reasons. If the medication is discontinued due to an AE, the AE should be followed up and recorded. Investigator should continue the participant's participation in the study as much as possible, resume the administration of the study drug as soon as possible while ensuring the safety of the participant, and record the date of discontinuation and re-administration (if the administration is interrupted for ≥ 4 consecutive weeks, the dose should be titrated from the initial dose; for other circumstances, Investigator will discuss with Sponsor before deciding the dose and titration regimen for resumption of administration).

In the event of the following situations, Investigator should discuss with Sponsor to

consider treatment suspension and decide whether to restart the study treatment based on the subsequent recovery of the participant and the safety risks of subsequent treatment:

- Abnormal hepatic function, meeting one of the following criteria:
 - ALT or AST $>8 \times$ ULN
 - ALT or AST $>5 \times$ ULN for more than 2 weeks
 - ALT or AST $>3 \times$ ULN and TBIL $>2 \times$ ULN or international normalized ratio ≥ 1.5
 - ALT or AST $>3 \times$ ULN with symptoms of fatigue, nausea, vomiting, right upper abdominal pain/tenderness, fever, rash, and/or eosinophilia ($>5\%$)
 - ALP $>3 \times$ ULN
 - ALP $>2.5 \times$ ULN and TBIL $>2 \times$ ULN
 - ALP $>2.5 \times$ ULN with symptoms of fatigue, nausea, vomiting, right upper abdominal pain/tenderness, fever, rash, and/or eosinophilia ($>5\%$)
- Calcitonin ≥ 50 ng/L (pg/mL)

4.6.2. Discontinuation of treatment

Discontinuation of study treatment does not represent withdrawal from the study.

If any of the following occurs, Investigator must discuss with Sponsor and consider treatment discontinuation, but the participant is allowed to continue with subsequent visits in the study:

- Participant decision: Treatment discontinuation requested by the participant;
- Increased risk of hypoglycemia: One episode of grade 3 hypoglycemia at any time during the treatment period or ≥ 2 symptomatic episodes of Grade 2 hypoglycemia within a week. Investigator must ensure that the participant has fully complied with the treatment regimen specified in the protocol, and after ruling out other possible causes of hypoglycemia (e.g., missed meals, increased exercise, etc.), Investigator may consider discontinuing the study drug;
- During the study treatment, when the BMI is ≤ 18.5 kg/m², Investigator should consider the risks of continuing the study treatment in full consideration according to the willingness of the participants and discuss with Sponsor whether treatment discontinuation is required;
- The participant is accidentally/wrongly enrolled and should not continue to receive the study drug after medical assessment;
- Acute or chronic pancreatitis;

- Diagnosed with medullary thyroid cancer after randomization;
- Active or untreated malignant tumors (except basal cell carcinoma/squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and carcinoma in situ of the prostate) diagnosed after randomization;
- Any hypersensitivity reaction clearly related to the study drug and intolerable by the participant;
- Other TEAEs, SAEs, or laboratory abnormalities that, in the opinion of Investigator, require discontinuation of the investigational product;
- Unnecessary risks of study drug continuation to the participant determined by Investigator and/or sponsor based on the participant's disease status or personal conditions.

Participants who discontinue the treatment are recommended to complete all visits and procedures according to the visit schedule, and should complete the early discontinuation visit at least 1 week ($\pm$ 3 days) after the last dose. If the decision to terminate the treatment has not been made at the V12 visit, the V12 primary endpoint visit should also be completed; if the early treatment discontinuation visit coincides with the V12 primary endpoint visit, only the V12 primary endpoint visit needs to be completed.

4.6.3. Withdrawal from study

Participants have the right to withdraw from the study at any time for any reason. The participant or the participant's guardian could have withdrawn consent at any time for any reason, or at Investigator's discretion. In addition, Investigator or sponsor may withdraw a participant from the study if enrollment into the study is inappropriate, in violation of the protocol, or for administrative and/or other safety reasons.

Participants should withdraw from the study and be recorded as withdrawal from the study in the following cases:

- Those who participated in other clinical trials during the trial. Participation in other trials is defined as having signed the informed consent form for other trials;
- Withdrawal of informed consent;
- Pregnancy of female participants;
- Investigator believes that the participant is not suitable to continue participating in this clinical trial.

The reason for withdrawal should be documented in the electronic case report form (eCRF).

Participants should complete the withdrawal visit before withdrawing from the study

and follow up the SAEs according to [Section 7.6.2](#).

4.7. Lost to follow-up

A participant will be considered lost to follow-up if he/she fails to return to the study site for at least 3 scheduled visits and is unable to be contacted by the study site personnel.

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

- The site will attempt to contact the participant and reschedule the missed visit 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, Investigator or designee will 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 attempts to contact the participant should be recorded in the participant's medical record or study documents.

If the participant is still out of contact, he/she will be considered lost to follow-up and withdrawn from the study.

5. Study Treatment and Concomitant Therapy

5.1. Treatment regimen

The study drugs include IBI362 and placebo, both of which are administered by subcutaneous injection in the abdomen QW. The treatment regimens used in this trial are shown in [Table 4](#).

Table 4. Treatment regimen

Study Groups	Treatment regimen	
	Double-blind treatment period	Study Extension Period
IBI362 4.0 mg group	IBI362 2.0 mg for 4 weeks + IBI362 4.0 mg for 20 weeks.	IBI362 4.0 mg, continuous administration for 24 weeks.
IBI362 6.0 mg group	IBI362 2.0 mg for 4 weeks + IBI362 4.0 mg for 4 weeks + IBI362 6.0 mg for 16 weeks.	IBI362 6.0 mg, continuous administration for 24 weeks.

Study Groups	Treatment regimen	
	Double-blind treatment period	Study Extension Period
Placebo group	The method of administration and dosage form for the 24-week continuous administration were consistent with those for the IBI362 group.	Switch to IBI362 2.0 mg for 4 weeks + IBI362 4.0 mg for 4 weeks + IBI362 6.0 mg for 16 weeks.

5.2. Study drug

5.2.1. Description of study drug

IBI362 injection (prefilled injection pen) is an injection with strengths of 0.5 mL:2 mg, 0.5 mL:4 mg, and 0.5 mL:6 mg. It is composed of the active ingredient IBI362 and excipients tromethamine, mannitol, propylene glycol (for injection), disodium edetate, dilute hydrochloric acid, sodium hydroxide, and water for injection. The primary packaging materials are a combination of prefilled syringe assembly and bromobutyl rubber stopper for prefilled syringe, and the secondary packaging materials are an automatic syringe assembly.

Placebo (prefilled injection pen) is an injection composed of excipients such as tromethamine, mannitol, propylene glycol (for injection), disodium edetate, dilute hydrochloric acid, sodium hydroxide, and water for injection. The primary packaging materials are a combination of prefilled syringe assembly and bromobutyl rubber stopper for prefilled syringe, and the secondary packaging materials are an automatic syringe assembly.

Manufacturer: Innovent Biologics (Suzhou) Co., Ltd.

5.2.2. Packaging and labeling of study drugs

The minimum packaging unit of IBI362 injection is box. Each box contains one vial of IBI362 injection packaged with a prefilled injection pen (0.5 mL: 2 mg, 0.5 mL: 4 mg, or 0.5 mL: 6 mg). The packaging of placebo is the same as that of IBI362.

The study drug package contains the protocol number, product name, drug number, strength, quantity, production batch number, expiry date, storage conditions, main components, dosage and administration, sponsor information, and precautions. The label on the prefilled injection pen contains the same information as the label on the box, but the label on the prefilled injection pen does not contain information on quantity, main ingredients, or precautions. All boxes and prefilled pens will be labeled "For Clinical Trial Use Only".

5.2.3. Preparation and use of study drug

IBI362 injection is packaged in pre-filled injection pens, and no additional preparation process is required before use.

This product is administered by subcutaneous injection into the abdomen.

Participants will receive training on the injection of the investigational product. If the participant is unable to self-administer the investigational product, the nursing staff should be trained and help the participant complete the investigational product administration.

5.2.4. Storage and stability of study drug

IBI362 needs to be stored under refrigeration conditions (2–8 °C), and the validity period is tentatively set to 36 months. If there are quality issues such as turbidity and precipitation in the injection, it should be sealed immediately and Innovent Biologics (Suzhou) Co., Ltd. should be notified immediately. See the drug manual for details.

5.3. Concomitant therapy

5.3.1. Definition of concomitant therapy

If there are other new concomitant medications during the study, Investigator should record the dosage and administration in a timely manner.

5.3.2. Prohibited concomitant therapy

The following treatments are prohibited during the study treatment period:

- Use of hypoglycemic therapy other than the study drug (except for meeting the rescue treatment criteria, after treatment discontinuation, or during the safety follow-up period);
- Chinese herbal medicines, other traditional medicines and health products with hypoglycemic effect indicated in the package insert (such as Tianqi Jiangtang Capsules, Jinlida Granules, Jinqi Jiangtang Tablets, Tianmai Xiaoke Tablets, Xiaoke Pills, Shenqi Jiangtang Granules, Gegen Qinlian Decoction, Dachaihu Decoction, etc.);
- Long-term (≥ 3 months) use of gastrointestinal motility inhibitors, including but not limited to anticholinergics, antiemetics, and opioids (e.g., metoclopramide, phenergan, dicycloverine, and morphine);
- Long-term (≥ 3 months) use of prokinetic agents (e.g., bethanechol, cisapride);
- Prescription or over-the-counter drugs with weight loss effects;
- Systemic glucocorticoid therapy for more than 14 consecutive days (except topical, intraocular, intranasal, and inhalational administration);
- central nervous system stimulants (e.g., methylphenidate hydrochloride);
- Any drug that has not been approved for marketing by regulatory authorities.

Investigator should review each drug (prescription and over-the-counter drugs) taken by the participant before the start of the study and at each study visit.

5.4. Rescue treatment

If the participant strictly follows the study protocol and is free from any acute disease that causes a sharp increase in blood glucose, and if the fasting blood glucose (FBG) level meets one of the following criteria, the participant should complete a FSG or FPG retest in the hospital on an empty stomach within 3 working days under the premise of maintaining a normal diet. If the retest result still meets one of the following criteria, Investigator may consider remedial treatment (prohibited GLP-1R agonists and DPP4 inhibitors).

- (1) FBG > 15.0 mmol/L from W2 to W6;
- (2) FBG > 13.3 mmol/L from W7 to W14;
- (3) FBG > 11.1 mmol/L from W15 to W48.

During the remedial treatment, Investigator may adjust the remedial drug according to the blood glucose level of the participant. Participants who receive rescue therapy should continue all subsequent visits per the protocol. New antidiabetic drugs added during the safety follow-up period will not be counted as rescue therapy.

In principle, the selection of remedial drugs and subsequent adjustments should follow the latest version of China guidelines for the prevention and treatment of type 2 diabetes mellitus.

5.5. Treatment compliance

Throughout the study, treatment compliance was monitored through drug dispensing and return records, medical records of participants, and diary cards.

The compliance to the study drug should be checked during the study. If there is any dose interruption, please describe it in the medical record.

5.6. Drug management

5.6.1. Study drug receipt and accountability

Sponsor will provide the study drugs (IBI362 and placebo) according to the expected enrollment plan of the study site. The study drugs will be delivered to the study site by a qualified third-party logistics company. The authorized staff of the study site will sign the shipment form to confirm receipt of the drugs.

The study drugs can only be used in this study. In order to fully control the distribution and use of the study drugs, the quantity needs to be registered at each visit.

5.6.2. Storage and management of study drug

The study drugs (IBI362 and placebo) should be refrigerated at 2-8 °C and cannot

be frozen. They should be transported to each study site by cold chain and kept and dispensed by a designated person.

The study drugs should be stored in a refrigerator that can only be opened by the authorized personnel. After receiving the drugs, the authorized personnel should confirm that the transportation temperature of the drugs is within the specified range, sign for receipt after verification, and store them at the specified temperature. If abnormal temperature occurs during transportation or storage at the study site, the drugs should be transferred to the specified temperature as soon as possible, and should not be used by the participants for the time being. The abnormal temperature should be reported to Sponsor in a timely manner and handled according to the opinions of Sponsor.

All study drugs provided by Sponsor should only be used for this study and should not be used for purposes other than those specified in this protocol. Investigator must promise not to provide the study drugs to anyone unrelated to this study.

5.6.3. Return and destruction of study drugs

In this study, used IBI362 and placebo containers should be recovered. If some study sites have difficulties in recovering the study drugs, they are allowed to destroy them on site with the consent of Sponsor.

Upon the completion or discontinuation of the study, all unused or expired study drugs must be returned to Sponsor for destruction. Arrangements for the return of study drugs were made by the clinical research associate (CRA) designated by Sponsor.

5.7. Study drug records

The designee of the study site should make timely records of receiving, dispensing, using, storing, returning, and destroying the study drugs in accordance with the requirements of relevant regulations and guidelines.

5.8. Complaint handling

To ensure the safety of study participants and the quality of monitoring, and to assist in improving the process and drug product, Sponsor will collect product complaints related to the investigational product used in the clinical trial.

Complaints regarding concomitant medications will be reported directly to the manufacturer according to the product description.

Investigator or designated personnel is responsible for completing the following product complaint procedures in accordance with the relevant provisions of this study:

- A drug complaint form specific for clinical trials should be used to document product complaints and relevant description completely.
- The completed product complaint form should be submitted to Sponsor or designated personnel by fax or email within 24 h.

- If Investigator is required to return the product for investigation, Investigator should return a copy of the product complaint form together with the product.

6. Study Assessments and Procedures

6.1. Efficacy assessments

6.1.1. Glycosylated hemoglobin

HbA1c samples will be collected as described in [Table 1](#), under fasted conditions. HbA1c at V1 and V3 will be tested at a local laboratory. Refer to the "Central Laboratory Manual" provided by Sponsor-designated central laboratory for sampling methods, sample storage, transportation, and analysis of HbA1c tests at other visits.

HbA1c samples will be transported to the central laboratory WuXi AppTec (Shanghai) Co., Ltd. for testing, and the remaining samples will be stored by WuXi AppTec (Shanghai) Co., Ltd. until 2 years after the drug is marketed and destroyed according to laboratory procedures.

6.1.2. Body weight

Body weights will be measured as described in [Table 1](#). Participants are required to fast, urinate, and remove their coats during each measurement. Participants should use a calibrated weight scale that is within the validity period of calibration each time, and avoid strenuous exercise before measurement. Refer to [Appendix 5](#) for detailed body weight measurement.

6.1.3. Waist circumference

Waist circumference will be measured according to [Table 1](#):

Standing position, relax both shoulders and abdomen, breathe steadily, and separate feet by 25-30 cm;

- Horizontal location of measurement: the midpoint of the line connecting the anterior superior iliac spine and the lower edge of the 12th rib at the midaxillary line;
- Wrap the tape around the abdomen in the above horizontal position, measure the tape tightly against the skin, but do not strangulate the skin;
- Waist circumference should be measured in cm to the nearest mm (e.g., 69.3 cm) at the end of a quiet exhalation without intentionally tucking or flexing the abdomen.

6.1.4. 7-point fingertip blood glucose

Fingertip blood glucose should be collected on an empty stomach, 2 h $\pm$ 30 min after breakfast, before lunch, 2 h $\pm$ 30 min after lunch, before dinner, 2 h $\pm$ 30 min after dinner, and before bedtime, and should be completed within 2 weeks before V4, V12, and V16.

For each 7-point fingertip blood glucose measurement, the measurements on two non-consecutive days should be collected. At least 1 complete 7-point fingertip blood glucose measurement should be provided before V4, V12, and V16. Participants are encouraged to monitor 4-point fingertip blood glucose every 2 weeks (before each meal and before bedtime).

6.1.5. Health outcome/quality of life assessments

To assess the physical condition of participants after continuous administration using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the European Quality of Life Five-Dimensions Five-Levels Scale (EQ-5D-5L)

6.1.6. Other efficacy evaluation indicators

Table 5. Laboratory tests for efficacy evaluation

Blood biochemistry	ALT, AST, uric acid
Blood Lipids	TC、TG、HDL-C、LDL-C
Glycemic control and insulin-related parameters	HbA1c, FPG, 1,5-AG, fasting insulin, and fasting C-peptide
Urine albumin/creatinine ratio	Urine albumin/creatinine ratio

6.2. Safety assessments

6.2.1. Laboratory tests

6.2.1.1. Laboratory test items

Table 6. Laboratory tests

Local laboratory test items	
Blood routine	White blood cell count, red blood cell count, platelets, hemoglobin concentration, hematocrit, differential white blood count (neutrophils, basophils, eosinophils, monocytes, and lymphocytes)
Blood biochemistry	ALT, AST, total bilirubin, direct bilirubin, albumin, total protein, glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase Serum potassium, serum sodium, serum calcium, serum chloride Uric acid, urea (or urea nitrogen), creatinine, eGFR, and creatine kinase (CK)
Routine urine test	Urine pH, urine protein, urine ketone body, urine glucose, urine red blood cells, and urine white blood cells
Viral serology	Hepatitis B panel & (HBsAg, HBsAb, HBcAb, HBeAb, HBeAg), HCV antibody, HIV antibody, and syphilis antibody (if HBsAg is positive, HBV-DNA test is required)

Blood Lipids	TC、TG、HDL-C、LDL-C
Thyroid Function	TSH、FT3、FT4
Other tests	HbA1c, serum calcitonin, blood amylase*, and blood lipase*
Central laboratory test items	
Other tests	Blood amylase, blood lipase, serum calcitonin, creatinine, and eGFR

*At least blood amylase test is required if the study site is limited

& Hepatitis B virus DNA test is required if the participant complains or is known to be positive for hepatitis B surface antigen.

6.2.1.2. Pregnancy test

Urine pregnancy or serum β -HCG pregnancy tests were performed for women of childbearing potential (as defined in Section of [Protocol 4.4.2.1](#)) according to the times in [Table 1](#). Blood/urine pregnancy test is applicable to women of childbearing potential, and blood pregnancy test is required at V1. In addition to the time scheduled in the visit schedule, a blood/urine pregnancy test should be performed if pregnancy is suspected during the study.

6.2.2. Clinical examination

6.2.2.1. Physical examination

A complete physical examination includes: general conditions, respiratory tract, cardiovascular system, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal system (including spine and limbs), genitalia/anus, and nervous system. Anogenital examinations were allowed to be omitted on an actual basis.

Refer to [Table 1](#) for examination time.

6.2.2.2. Vital signs

Vital signs will be performed as described in [Table 1](#). Vital signs include body temperature, pulse, respiratory rate, and blood pressure.

Instructions for blood pressure measurement:

Blood pressure can be measured with a mercury column sphygmomanometer or an electronic sphygmomanometer.

At the screening visit, blood pressure was measured in both arms. If the difference in systolic or diastolic blood pressure between the arms is greater than 10 mmHg, the arm with the higher blood pressure measured at the screening visit must be used for blood pressure measurements at subsequent visits.

Blood pressure must be continuously measured throughout the study. The blood pressure should be measured on the same arm selected for the screening visit at each visit

(except for special circumstances where the same arm cannot be measured for objective reasons).

Participants should rest for at least 5 min before measurement. The measurement should be repeated twice. After the first blood pressure measurement, it should be measured again after an interval of at least 1 min. The mean blood pressure will be calculated based on the two measurements. If the difference between the 2 systolic or diastolic blood pressure readings is more than 5 mmHg, the measurement should be repeated, and the mean blood pressure should be calculated based on the 3 measurements.

6.2.2.3. 12-lead ECG

The resting 12-lead ECG will be analyzed at the local laboratory according to the schedule of visits in [Table 1](#).

A 12-lead ECG was performed after the participant had rested for at least 5 minutes. All 12-lead ECGs should be performed while the participant is resting in the supine position. 12-lead ECG indicators include RR interval, PR interval, heart rate (HR), QT interval, and QTcF ($QTcF = QT/RR^{0.33}$). If the participant has ECG abnormalities, Investigator can perform additional ECGs according to the actual situation. Further ECG will be performed if clinically indicated, such as a cardiac AE. On the day of ECG examination, Investigator completed the ECG assessment and recorded the assessment results on the ECG. The same method of assessment should be used throughout the study. 15-lead or 18-lead ECGs may be substituted for 12-lead ECGs depending on the site's equipment.

6.2.2.4. Dilated fundoscopy

According to the schedule of visits in [Table 1](#), all participants will undergo dilated fundoscopy by professionals (fundoscopy is not repeated during the screening period if the participant can provide a fundus examination report within 3 months before screening) to rule out proliferative diabetic retinopathy, diabetic macular edema, or nonproliferative diabetic retinopathy requiring urgent treatment. If the conditions for pupil dilation are not met, fundus photos or ultra-widefield fundus photos can be used instead.

6.3. Collection and analysis of pharmacokinetic specimens

PK samples will be collected according to Schedule of Visits [Table 1](#). 3 mL of peripheral blood will be collected at each blood sampling time point. Refer to the "Central Laboratory Manual" provided by Sponsor-designated central laboratory for sampling methods, sample storage, transportation, and analysis.

PK samples should be collected from all participants at the blood sampling points specified in the protocol, and serum drug concentrations should be measured from all participants in the IBI362 group.

6.4. Immunogenicity

Immunogenicity samples will be collected according to [Table 1](#), with 5 mL of peripheral blood collected at each blood sampling time point. Refer to the "Central Laboratory Manual" provided by Sponsor-designated central laboratory for sampling methods, sample storage, transportation, and analysis.

Immunogenicity samples should be collected from all participants at the blood sampling points specified in the protocol, and the samples from all participants in the IBI362 group will be tested for immunogenicity. If necessary, the concentration of IBI362 in immunogenicity samples will be determined.

6.5. Storage and destruction of biological samples

Biological samples will be used for the tests specified in this protocol. If needed, individual or pooled samples may be used for further evaluation and validation of the assay. The results of these analyses may be included in the clinical study report (CSR) or reported separately from the CSR.

Sample reproducibility analysis can be performed simultaneously with biological sample testing. The reproducibility analysis results will not be recorded in the CSR but will be presented in the bioanalytical report. After all necessary analyses are completed, the individual information will be desensitized (including anonymization and sample merging) and then processed and destroyed.

6.6. Unscheduled visit

Unscheduled visits may be performed at the request of the participants or Investigator. Investigator will conduct relevant examinations according to the conditions of the participants, including but not limited to: vital signs, targeted physical examinations, hematology/blood biochemistry/urinalysis, and imaging evaluation. All test results from unscheduled visits should be recorded in the eCRF.

7. Safety Reporting and Adverse Event Management

7.1. Definition of adverse events

An adverse event (AE) is defined as any adverse medical event that is observed after the signing of the informed consent form, regardless of whether or not considered as related to the investigational product. AEs include but are not limited to the followings:

- Worsening of pre-existing (prior to enrollment) medical conditions/diseases (including symptoms, signs, and laboratory test abnormalities);
- Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);
- Clinically significant abnormal laboratory findings.

7.2. Adverse events of special interest

Special attention was paid in this study to the following AEs that occurred after the first dose: severe gastrointestinal reactions (nausea, vomiting, diarrhea), hypoglycemic events, acute pancreatitis, thyroid malignancy and thyroid C-cell hyperplasia, major adverse cardiovascular events, supraventricular tachycardia and conduction block, allergic reactions and injection site reactions, diabetic retinopathy complications, acute kidney injury, and acute gallbladder disease. In this clinical study, Investigator should pay close attention to whether the participants experience the above AEs. The above AEs that occur after the first dose should be recorded as AESIs and treated in a timely manner.

7.2.1. Severe gastrointestinal reactions (nausea, vomiting, diarrhea)

Severe gastrointestinal reactions (nausea, vomiting, and diarrhea) are AEs of special interest and will be recorded as AEs in the eCRF (severity is uniformly recorded according to NIA standards). Each event should be assessed for severity, duration (start and end dates), and causality with the investigational product or protocol procedures as judged by Investigator. The grading criteria are shown in [Table 7](#). CTCAE Grade 1: mild; CTCAE Grade 2: moderate; CTCAE Grade ≥ 3 : severe.

Table 7.. Grading criteria (CTCAE/NIA).

Gastrointestinal reactions	CTCAE grade				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Decreased appetite without changes in eating habits	Reduced oral intake without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition, or hospitalization indicated	-	-
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, total parenteral nutrition, or hospitalization indicated	Life-threatening	Death
DIARRHEA	Increase of < 4 stools per day over baseline;	Increase of 4-6 stools per day over baseline;	Increase of ≥ 7 stools per day over baseline; hospitalization	Life-threatening consequences; urgent	Death

Gastrointestinal reactions	CTCAE grade				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	mild increase in ostomy output compared to baseline	moderate increase in ostomy output; limiting instrumental ADL	indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	intervention indicated	
Corresponding to NIA standard					
Severity Grade	Mild	Moderate	Severe		

7.2.2. Hypoglycemic episodes

Investigator will determine whether a hypoglycemic event is severe hypoglycemia based on the patient's need for medical assistance other than the expected assistance routinely received. All hypoglycemic events will be recorded in the hypoglycemia module of the electronic event report form, while all severe hypoglycemic events must be reported as SAEs.

To avoid repeated reporting, all continuous blood glucose levels < 3.9 mmol/L within 1 h were considered as a single hypoglycemic event.

Hypoglycemia grading criteria:

- **Grade 1 hypoglycemia:** 54 mg/dL (3.0 mmol/L) ≤ blood glucose <70 mg/dL (3.9 mmol/L)
- **Grade 2 hypoglycemia:** blood glucose <54 mg/dL (3.0 mmol/L)
- **Grade 3 hypoglycemia (severe hypoglycemia):** Refers to situations in which the participant requires assistance from another person to obtain carbohydrate, glucagons, or other rescue measures. During this period, the patient develops a change in state of consciousness, is unable to take care of the above-mentioned restorative treatment, is unconscious or semi-conscious, or develops coma (whether accompanied by epileptic seizure symptoms) and requires intravenous nutritional supplements. For such events, blood glucose measurements may not be recorded, but neurological symptoms may recover as blood glucose returns to normal, which fully proves that such events are caused by hypoglycemia.

During the study, if a participant experiences symptom of hypoglycemia at home, such as hunger, generalized weakness, dizziness and headache, cold hands and feet, cold sweats, general shivers, and coma, it is recommended to contact Investigator in time and come to the hospital for examination and reasonable treatment as soon as possible

according to the actual situation.

7.2.3. Pancreatitis acute

Serum amylase and lipase are monitored at protocol-specified timepoints and may be added at Investigator's clinical discretion.

When blood amylase and / or lipase $\geq 3 \times$ ULN, further diagnostic evaluation is required even if the participant has no symptoms of acute pancreatitis (refer to [Appendix 3](#)).

7.2.4. Malignant neoplasm of thyroid gland and thyroid C-cell hyperplasia

All participants with a history or family history of medullary thyroid cancer or multiple endocrine neoplasia (MEN) 2A or 2B during the screening period will be excluded. At the same time, calcitonin levels will be regularly monitored during the trial to assess the possibility of thyroid C cell hyperplasia or thyroid malignancy.

If post-randomization calcitonin is ≥ 50 ng/L (pg/mL), consider interrupting the study drug and consulting a thyroid surgeon or endocrinologist for further treatment. If a participant takes a non-study drug that causes calcitonin increased, the drug should be discontinued without compromising the participant's safety, and calcitonin should be retested after an appropriate washout period. In any of the above cases, Investigator should report the relevant AEs and record them in the CRF. If the calcitonin of the above participants returns to < 35 ng/L (pg/mL) in the future, Investigator may consider whether to restart the study drug after assessing the safety.

7.2.5. Major cardiovascular events

Cardiovascular death and non-fatal cardiovascular events were all adjudicated by an external CEC committee independent of Sponsor for the following five categories of cardiovascular events: cardiovascular death, non-fatal acute myocardial infarction, ischemic stroke, hospitalization for heart failure, and hospitalization for unstable angina. The specific procedures and definitions are described in the CEC Charter.

7.2.6. Supraventricular tachycardia and conduction block category disorders

New cases of supraventricular tachycardia and conduction block during treatment (without previous relevant diseases and not present at baseline) should be reported as AEs. At the same time, conduction block diseases need to be clearly classified, such as first-degree atrioventricular block, second-degree type I atrioventricular block, complete left bundle branch block, etc. If the ECG is not clear, a cardiologist should assist in making a clear diagnosis and assessing the need for intervention if necessary.

7.2.7. Allergic reactions and injection site reactions

7.2.7.1. Allergic reaction

Acute onset within minutes to hours:

- Skin and/or mucosal symptoms (angioedema, urticaria, eczema)
- Respiratory symptoms (dyspnea, wheezing, and bronchospasm)
- Hypotension (SBP 30% decrease from baseline)

7.2.7.2. Injection site reaction

Injection site reactions include symptoms such as injection site swelling, flushing, ecchymosis, pruritus, induration, and pain (except for prickling pain and transient pain).

If a participant experiences an injection site reaction or allergic reaction, it is recommended that the participant come to the hospital to collect immunogenicity blood samples at the following time points as far as possible: at the beginning of the event, at the end of the event, and 30 days ($\pm$ 3 days) after the end of the event. A total of 5 mL of whole blood will be collected at each blood sampling time point. Refer to the central laboratory manual for details.

7.2.8. Diabetic retinopathy complications

During the screening period, dilated funduscopy and/or optical coherence tomography (OCT) will be performed for all participants to exclude patients with proliferative diabetic retinopathy, diabetic macular edema, or nonproliferative diabetic retinopathy requiring urgent treatment.

Investigator may perform additional tests on participants with any suspected AE related to retinopathy during the study and record the results in the CRF.

7.2.9. Acute kidney injury

During the study, the overall renal safety will be assessed based on the regular monitoring of changes in renal function and the reporting of renal AEs. Nausea, vomiting, and diarrhea may lead to dehydration, which may result in deterioration of renal function, including acute renal failure. It is recommended that the participant seek medical attention promptly in case of severe nausea, frequent vomiting, or dehydration and complete relevant examinations. Relevant results should be recorded in the CRF.

KDIGO Clinical Practice Guideline for Acute Kidney Injury Definition of Acute Kidney Injury:

- Blood creatinine increased by ≥ 0.3 mg/dL (>26.5 $\mu\text{mol/L}$) within 48 h
- An increase in blood creatinine to ≥ 1.5 times the baseline value that is known or presumed to have occurred within 7 days
- Urine volume <0.5 mL/kg/hr for 6 hours

Staging of acute kidney injury:

Stage	Blood creatinine	Urine Volume
1	Increase by 1.5 to 1.9 times the baseline value; or increase by ≥ 0.3 mg/dL (>26.5 μ mol/L)	<0.5 mL/kg/h for 6 ± 12 h
2	Increase by 2.0–2.9 times the baseline value	<0.5 mL/kg/h, lasting ≥ 12 h
3	Increase by 3.0 times the baseline value; or Increase by ≥ 4.0 mg/dL (353.6 μ mol/L); or Initiation of renal replacement therapy; or Decrease in eGFR to <35 mL/min/1.73 m in patients aged <18 years ²	<0.3 mL/kg/h for ≥ 24 hours; or anuria for ≥ 12 h

7.2.10. Acute gallbladder disease

If biliary colic, cholecystitis, or other suspected gallbladder-related adverse events occur during the study, relevant examinations should be added according to the actual situation. Acute gallbladder diseases mainly include biliary colic, acute cholecystitis or acute attack of chronic cholecystitis, cholelithiasis (except chronic gallstones), cholecystectomy, etc.

7.3. Definition of serious adverse event

An SAE refers to an AE that meets at least one of the following criteria:

- Results in death;
- Life-threatening (a life-threatening event is defined as an AE when the participant is at immediate risk of death at the time, but does not include the case that may lead to death only when the event worsens);
- Hospitalization or prolonged hospitalization, excluding the following:
 - Rehabilitation facilities;
 - Nursing homes;
 - General emergency admission;
 - Day surgery (such as outpatient/same-day/ambulatory surgery);
 - Hospitalization or prolonged hospitalization unrelated to the worsening of an AE is not an SAE. Hospitalization due to pre-existing disease, without new AEs or exacerbation of pre-existing disease (e.g. hospitalization to examine laboratory abnormalities that have been persistent before the study starts); hospitalization for administrative reasons (e.g. annual routine physical examinations); hospitalizations during the study as specified in the protocol (e.g. hospitalization performed in accordance study protocol); elective hospitalization unrelated to worsening of AEs (e.g. elective

surgery); scheduled treatment or surgical procedures, which should be documented in the entire study protocol and/or individual participant's baseline information; and hospitalization merely due to the use of blood products.

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in a congenital anomaly/birth defect (in the child of a participant who used the product).

Other important medical events: events that may not result in death, be life-threatening, or require hospitalization but may jeopardize the participant and may require medical or surgical intervention to prevent any one of the above outcomes based on appropriate medical judgment. For example, severe hypoglycemic events (refer to [Section 7.2.2](#)).

7.4. Assessment of severity of adverse events

Investigators will judge the severity according to the grading criteria for adverse events issued by the National Institute on Aging (NIA).

- Mild: Awareness of signs or symptoms that are easily tolerated and are of a minor irritant type that does not interfere with normal activities, does not require treatment or medical evaluation, and are transient in nature.
- Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved with simple therapeutic measures; moderate adverse events may cause some functional impairment.
- Severe: The event interrupts the participant's normal daily life and usually requires systemic medication or other treatment, which is usually incapacitating.

7.5. Determination of the causal relationship between adverse events and the investigational product

For adverse events in clinical trials. Investigator with medical qualifications is required to provide an assessment of the causal relationship between the investigational product and the AE. The elements in [Appendix 4](#) were used to assess the causal relationship between the study drug and adverse events.

7.6. Recording of adverse events

Investigator should use medical terms/concepts to record AEs or SAEs. Colloquial language and abbreviations should be avoided. All AEs (including SAEs) should be recorded on the AE form of the eCRF.

7.6.1. Collection and time of adverse events

Investigator should learn about AEs by asking the participants non-leading questions.

All AEs, including SAEs, that occur from the signing of the informed consent form until the end of the study will be collected, regardless of whether they are observed by Investigator or self-reported by the participant.

AESIs will be collected from the first dose of the study drug until the end of the study.

7.6.2. Follow-up of adverse events

AEs should be followed up until the events return to the baseline or until Investigator believes that no further follow-up is required for reasonable reasons (if the events cannot be resolved or have already been improved). If the AE cannot be recovered, a reasonable explanation should be recorded in the eCRF. The outcome of an AE/SAE and date should be documented in the eCRF and medical record, regardless of whether the event is related to the investigational product.

7.6.3. Contents of AE documentation

Investigator must document all the AEs, including the diagnosis (document signs and symptoms including the laboratory abnormalities if there is no diagnosis), time and date of occurrence (if applicable), severity, changes, whether it is an SAE, whether it is an AE of special interest (AESI), measures taken for the study drugs, treatment for the AE, outcome of the event, and relationship between the event and study drugs.

For an SAE, Investigator should also provide the date when the AE meets the criteria for an SAE, the date when Investigator is informed of the SAE, the reason why the AE is an SAE, the date of hospitalization, the date of discharge, the possible cause of death, the date of death, whether an autopsy has been performed, the causality assessment of the study procedures, the causality assessment of other drugs, and other possible causes of the SAE. Investigator should also provide the rationale for the causality and a description of the SAE. In the SAE description, the followings shall also be included: the participant number, age, gender, height, and weight; indication for receiving the study drug, cancer staging, and overall condition; SAE occurrence, development, outcome, and result; laboratory results related to the SAE (the time of the examination, units, and normal ranges must be provided); medical history, onset and duration of concurrent diseases related to the SAE; medication history and initiation, duration, and dosage of concomitant medications related to the SAE; initiation, duration, and dosage of the study drug.

The description of AE recording is as follows:

Diagnosis, signs, and symptoms

If a diagnosis has been made, the diagnosis rather than individual symptoms and

signs should be recorded in the eCRF (e.g., hepatic failure rather than jaundice, transaminases increased, and asterixis should be recorded). If the symptoms and signs cannot be confirmed to be caused by the diagnosis at the time of reporting, they should be recorded as separate AEs/SAEs. If it is determined that the symptoms and signs are caused by the diagnosis, only the diagnosis will be reported separately and the symptoms and signs will be included in the diagnosis. The record of symptoms and signs should be deleted for an AE, and a follow-up update report should be sent for an SAE.

Adverse events secondary to other events

Generally, for AEs secondary to other events (e.g., caused by other events or clinical sequelae), the primary event should be recorded, unless the secondary event is severe or an SAE. However, clinically significant secondary events should be recorded as independent AEs in the eCRF if they occur at a different time from the primary event. If the relationship between events is unclear, they should be recorded separately in the eCRF.

Persistent or recurrent adverse events

Persistent AEs refer to AEs that persist without relief between two evaluation time points.

Recurrent AEs refer to AEs that have resolved between the two evaluation time points but subsequently occur again. The occurrence of the events should be recorded separately in the eCRF.

Laboratory abnormalities

Clinically significant laboratory abnormalities should be reported as AEs. Investigator is responsible for reviewing all laboratory abnormalities and determining whether the abnormalities should be reported as AEs.

Pre-existing medical conditions

Symptoms/signs present during the screening period will be recorded and reported as AEs only if their severity, frequency, or property becomes aggravated (except for worsening of the studied disease). Changes from the previous status should be reflected in the record, such as "increased headache frequency".

Death

Death that occurs from the signing of the informed consent form to the completion of the study (completion of follow-up or withdrawal) should be recorded in the death report form of the eCRF and reported to Sponsor timely, regardless of whether it is related to the investigational product. Death of a participant after the completion of the study is not required to be reported as an SAE unless it is considered to be related to the investigational product or study procedures.

For a death with a known cause, record the cause of death as an AE and the outcome

of the AE as "death" and submit an SAE report; for a death with an unknown cause, the AE shall be recorded as "Death of unknown cause" in the AE form of the eCRF, and "Death of unknown cause" as the SAE report. The exact cause of the death shall then be further investigated.

Hospitalization, prolonged hospitalization, or surgery

Any AE that results in hospitalization or prolonged hospitalization should be recorded and reported as an SAE, except for the following:

- Planned hospitalization or prolonged hospitalization as required by the protocol (e.g., for administration, efficacy evaluation, etc.).
- Hospitalization due to pre-existing medical conditions that have not changed before participating in the study. e.g., elective surgery/treatment scheduled prior to study participation.

However, if the disease worsens during the study (e.g., surgery/treatment is required earlier than scheduled), then the elective surgery/treatment due to disease worsening is considered as an AE.

Overdose

A dose exceeding 20% of the dose specified in the protocol is considered an overdose. Overdose will be recorded in the eCRF.

7.7. Expedited reporting of SAEs and pregnancy

7.7.1. SAE reporting

SAEs that occur from the signing of the informed consent form to the end of the study should be reported. If a participant/participant experiences an SAE, Investigator must immediately report it to Sponsor's pharmacovigilance department within 24 hours after becoming aware of the SAE in the manner and according to the requirements specified by Sponsor. For any questions, please contact the public email address of Sponsor's pharmacovigilance department: drugsafety@innoventbio.com.

For deaths and life-threatening serious adverse events, Investigator should urgently follow up the missing information and provide a complete SAE report.

If an SAE occurring outside of the above-mentioned period is determined to be related to the study drug, it should also be reported to Sponsor.

7.7.2. Pregnancy

It is not known whether there is a safety risk of embryotoxicity in such drugs. All participants of childbearing potential participating in this clinical study must take effective contraceptive measures.

During the clinical study, if a female participant exposed to the study drug becomes

pregnant, Investigator should report the pregnancy to Sponsor within 24 h of awareness in the manner and according to the requirements specified by Sponsor.

During the clinical study, male participants who are exposed to the study drug can continue the clinical study if their partners become pregnant. Investigator should report the pregnancy to Sponsor within 24 h of awareness in the manner and according to the requirements specified by Sponsor.

Investigator should continuously monitor and follow up on the outcome of the pregnancy until 8 weeks after the participant gives birth. The outcome should be reported to Sponsor.

Pregnancy outcomes such as stillbirth, spontaneous abortion, fetal malformation (any congenital anomaly/birth defect), and medical abortion are considered as SAEs and should be reported according to SAE procedures and time limits.

If a participant experiences any SAE during pregnancy, the SAE should be reported according to the procedures for reporting SAEs.

8. Statistical Considerations

8.1. Statistical analysis plan

A detailed statistical analysis plan (SAP) will be written after the first participant is enrolled and finalized before the database is frozen for the primary endpoint analysis. The SAP will provide all analyses to be performed in this trial and the expression methods of the results.

8.2. Hypothesis test

Take the primary endpoint as an example:

At week 24, change in HbA1c in the IBI362 group from baseline: μ_{IBI362} ;

Change in HbA1c from baseline at week 24 in the placebo group: μ_{placebo} ;

$H_0: \mu_{\text{IBI362}} \geq \mu_{\text{placebo}}$

$H_a: \mu_{\text{IBI362}} < \mu_{\text{placebo}}$

The hypothesis of superiority will be tested by a two-sided test at $\alpha = 0.05$. The superiority of IBI362 group vs. placebo group will be tested for the following endpoints in the order listed below.

- Change in HbA1c from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Change in HbA1c from baseline at week 24 (IBI362 4.0 mg vs. placebo);
- Proportion of participants with HbA1c <7.0% at week 24 (IBI362 6.0 mg vs. placebo);

- Proportion of participants with HbA_{1c} <7.0% at week 24 (IBI362 4.0 mg vs. placebo);
- Proportion of participants with HbA_{1c} <7.0% and ≥5% weight reduction from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Proportion of participants with HbA_{1c} <7.0% and ≥5% weight reduction from baseline at week 24 (IBI362 4.0 mg vs. placebo);
- Proportion of participants with ≥5% weight loss from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Proportion of participants with ≥5% weight loss from baseline at week 24 (IBI362 4.0 mg vs. placebo);
- Percent change in body weight from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Percent change in body weight from baseline at week 24 (IBI362 4.0 mg vs. placebo).

The efficacy differences between each IBI362 dose group and the placebo group at each endpoint will be compared sequentially. If this endpoint is significant ($p < 0.05$), it can be considered that this IBI362 dose group is statistically superior to the placebo group at this endpoint, and the comparison of the next endpoint can be performed. If the comparison is not significant ($p \geq 0.05$), it is considered that the statistical superiority of IBI362 dose group over the placebo group on this endpoint is not established, and the inter-group comparison on any endpoint after the endpoint sequence is not conducted.

All between-group comparisons were performed in parallel at the two estimands, $\alpha = 0.05$. No multiplicity adjustment will be performed between the two estimands.

8.3. Sample size estimation

Assuming that HbA_{1c} in the IBI362 4.0 mg/6.0 mg group after 24 weeks of continuous treatment is decreased by 1.6% and 1.7%, respectively, and HbA_{1c} in the placebo group is decreased by 0.3% with a standard deviation of 1.2% and $\alpha = 0.05$ (two-sided), this study plans to enroll 300 participants with no more than 330 participants. The participants will be randomized in a 1:1:1 ratio into 3 treatment groups, namely the IBI362 4.0 mg group, the IBI362 6.0 mg group, and the placebo group. The stratification factor is HbA_{1c} level prior to randomization (V3) (HbA_{1c} <8.5% or HbA_{1c} ≥8.5%). With a power of 99% or greater, statistical superiority of any IBI362 dose group to the placebo group can be observed.

8.4. Statistical analysis populations

Intent to treat (ITT) set: All randomized participants. The analysis of this

population will be based on the treatment group to which the participant is randomized.

Modified intent to treat (mITT) set: Participants who were randomized and received at least one dose of the study drug. The analysis of this population will be based on the treatment group to which the participant is randomized.

Per protocol set (PPS): Participants in the revised intention-to-treat set who have no major protocol violations that affect the efficacy evaluation.

PK analysis set: includes all participants who have received at least one dose of the investigational product and have at least one valid post-dose concentration data of the test component.

Safety set (SS): Participants who have received at least one dose of the study drug after randomization. Participants will be analyzed by group according to the study drug they actually received.

8.5. Statistical analysis methods

8.5.1. General methods of statistical analysis

Continuous data will be described by mean, standard deviation, median, maximum, and minimum; categorical data will be described by frequency and percentage. All statistical analyses will be performed using SAS v9.4 (or higher).

If the baseline is missing, it will be imputed with the mean baseline measurement result of the same group.

8.5.2. Efficacy analyses

Efficacy analyses will be performed on the mITT.

Descriptive summary of observed values will be provided for each efficacy endpoint by visit. Measurement data will be described by mean, standard deviation, median, maximum, and minimum; enumeration data will be described by frequency and percentage.

In the application for marketing registration, the analysis will be mainly based on the treatment estimand. If the primary endpoint is reached under the treatment estimand, the study is considered to obtain a positive result, and the application for marketing registration of IBI362 will be submitted. The analysis based on the efficacy estimand will be used as supporting evidence for non-registration purposes, such as publication of research papers. No multiplicity adjustment will be made between the two estimands.

The type of intercurrent event and the time point of occurrence will be determined by directly grabbing the corresponding information on the corresponding page of the CRF. If the same participant has experienced two intercurrent events in succession, the earlier intercurrent event will be classified. If two intercurrent events occur at the same time, they will be classified according to the use of remedial treatment.

8.5.2.1. Analysis of primary endpoint

The primary endpoint of this trial was the change in HbA1c from baseline at week 24.

- **Analysis of the Primary Endpoint Indicator for the Treatment-policy Estimand**

An analysis of covariance (ANCOVA) will be used, which includes treatment group and randomization stratification factors as fixed effects and baseline HbA1c as a covariate in the model. The corrected least squares estimates of the mean changes in HbA1c from baseline in the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group and their 95% CIs were calculated, and the inter-group difference estimates, corresponding standard errors, 95% CIs, and corresponding p-values of the two IBI362 dose groups vs. the placebo group were provided.

Intercurrent events and handling of intercurrent events:

Intercurrent events were premature discontinuation of treatment and use of rescue therapy for any reason. Intercurrent events are handled using the treatment policy strategy, i.e., data collected after the intercurrent event is continued to be used. In case of missing data in the data collected after the occurrence of intercurrent events, multiple imputation will be performed using the data of participants in the same treatment group (IBI362 group or placebo group) who have experienced intercurrent events but have HbA1c measurement results collected at Week 24. If intercurrent events occur but there are too few data from participants in the same treatment group with HbA1c measurements collected at Week 24 resulting in non-convergence of the model, multiple imputation will be performed using all data from participants in the same group with HbA1c measurements collected.

Imputation of missing values not due to intercurrent events:

For missing values not due to an intercurrent event, multiple imputation will be performed using data from all participants in the same group for whom HbA1c measurements are collected.

Sensitivity analysis:

- For missing data after the intercurrent event, multiple imputation will be performed using the data of participants in the same group who have experienced the intercurrent event but whose HbA1c measurement results at Week 24 are collected (if the model does not converge due to too little data of participants in the same treatment group who have experienced the intercurrent event but whose HbA1c measurement results at Week 24 are collected, multiple imputation will be performed using the data of all participants in the same group whose HbA1c measurement results are collected); for missing values not caused by the intercurrent event, J2R (Jump to Reference) will be used for multiple

imputation. That is, for participants who do not experience intercurrent events but have missing HbA1c measurements at Week 24, regardless of treatment group, the missing data will be multiply imputed using HbA1c measurements collected from the placebo group.

- Missing data after the intercurrent event and missing values not caused by the intercurrent event will be imputed using last observation carried forward (LOCF).
- The sensitivity analysis will be performed using the methods of return to baseline (RTB) and tipping point, which will be described in detail in the SAP.

Supplementary analysis:

- Supplementary analysis was performed using the PPS.

Other sensitivity and supplementary analyses will be described in detail in the SAP.

- **Analysis of Primary Endpoint Indicator for Efficacy Estimand**

MMRM will be used, with treatment group, visit, treatment group-by-visit interaction, and randomization stratification factors as the fixed categorical effects, and baseline HbA1c as the covariate. The corrected least squares estimates of changes in HbA1c from baseline and their 95% CIs in the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group will be calculated, respectively, and the inter-group difference estimates, corresponding standard errors, 95% CIs, and corresponding p-values of the two IBI362 dose groups vs. the placebo group will be provided.

Intercurrent events and handling of intercurrent events:

Intercurrent events were premature discontinuation of treatment and use of rescue therapy for any reason. Data after the occurrence of an intercurrent event will not be included in the analysis, and the intercurrent event will be handled using a hypothetical strategy, assuming that no participants in the study experience drug efficacy in the event of an intercurrent event. Data after the occurrence of intercurrent events will be imputed using the method for missing at random (MAR) built into the MMRM model SAS.

Imputation of missing values not due to intercurrent events:

Missing data not caused by intercurrent events will also be imputed using the MAR method built into the MMRM model of SAS.

Sensitivity and supplementary analyses will be described in detail in the SAP.

8.5.2.2. Analysis of secondary endpoints

- **Analysis of Key Secondary Endpoints by Category**

The categorical key secondary endpoints for this study were at week 24:

- Proportion of participants with HbA_{1c} <7.0%;
- Proportion of participants with HbA_{1c} <7.0% and weight loss of ≥5% from baseline;
- Proportion of participants who lose ≥5% of their body weight from baseline.

Analyses Under the Treatment Estimand

Logistic regression will be used. In the model, treatment group and randomization stratification factor will be used as fixed effects, and the baseline value of the corresponding indicator will be used as a covariate. The odds ratio (OR) and its 95% CI of IBI362 4.0 mg group and IBI362 6.0 mg group vs. placebo group, as well as the corresponding p value, will be provided. The inter-group difference in the achievement rate of two IBI362 dose groups vs. the placebo group and its 95% CI will be calculated. Success was calculated for each group and the corresponding 95% CI was provided.

Intercurrent events and handling of intercurrent events:

Intercurrent events were premature discontinuation of treatment and use of rescue therapy for any reason. Intercurrent events will be handled using the treatment policy strategy, i.e., data collected after the intercurrent event will continue to be used. If there are missing data in the data collected after the occurrence of intercurrent events, multiple imputation will be performed using the data of participants in the same treatment group (IBI362 group or placebo group) who have experienced intercurrent events but have collected the measurement results of corresponding indicators, and then the achievement will be derived according to the imputed continuous variables.

Imputation of missing values not due to intercurrent events:

For missing values not caused by intercurrent events, multiple imputation will be performed using all the data of participants in the same group whose measurements are collected for the corresponding indicators. The success is then derived based on the imputed continuous variable.

Sensitivity analysis:

- For missing data after the intercurrent event, multiple imputation will be performed using the data of participants in the same group who have experienced the intercurrent event but have collected the corresponding measure; for missing values not caused by the intercurrent event, J2R will be used for multiple imputation. That is, for participants who do not experience intercurrent events but have missing measurements of the corresponding measure regardless of treatment group, the missing data will be multiply imputed using the corresponding measure collected from the placebo group. The success is then derived based on the imputed continuous variable.

- Missing data after intercurrent events and missing values not due to intercurrent events will be imputed using LOCF.
- Missing data after the occurrence of the intercurrent event and missing values not caused by the intercurrent event will be imputed as non-responder (NR), i.e., the corresponding indicator is not met.
- The sensitivity analysis will be performed after the corresponding continuous variables are imputed and dichotomized using methods such as RTD, which will be described in detail in the SAP.

Supplementary analysis:

- The PPS was used for supplementary analysis.

Other sensitivity and supplementary analyses will be described in detail in the SAP.

Analyses Under the Efficacy Estimand

Logistic regression will be used. In the model, treatment group and randomization stratification factor will be used as fixed effects, and the baseline of the corresponding indicator will be used as a covariate. The OR and its 95% CI as well as the corresponding p value of IBI362 4.0 mg group and IBI362 6.0 mg group vs. placebo group will be provided. The inter-group difference in the achievement rate of two IBI362 dose groups vs. the placebo group and its 95% CI will be calculated. Success was calculated for each group and the corresponding 95% CI was provided.

Intercurrent events and handling of intercurrent events:

Intercurrent events were premature discontinuation of treatment and use of rescue therapy for any reason. Data after the occurrence of an intercurrent event will not be included in the analysis, and the intercurrent event will be handled using a hypothetical strategy, assuming that no participants in the study experience drug efficacy in the event of an intercurrent event. Data after an intercurrent event will be assumed to be missing at random (MAR), using multiple imputation (MI) under the MAR mechanism, and will derive its success based on the imputed values.

Imputation of missing values not due to intercurrent events:

Missing data that are not caused by intercurrent events will be assumed to be missing at random (MAR), using multiple imputation (MI) under the MAR mechanism, and then its compliance will be derived based on the imputed values.

Sensitivity and supplementary analyses will be described in detail in the SAP.

• **Analyses of Continuous Key Secondary Endpoints**

The continuous key secondary endpoint for this study was percent change from baseline in body weight at 24 weeks.

Analyses Under the Treatment Estimand

ANCOVA will be used with treatment group and randomization stratification factors as fixed effects and baseline body weight as a covariate in the model. The corrected least squares estimates of the mean percentage change in body weight from baseline in the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group and their 95% CIs were calculated, and the inter-group difference estimates, corresponding standard errors, 95% CIs, and corresponding p values of the two IBI362 dose groups vs. the placebo group were provided.

Intercurrent events and handling of intercurrent events:

Intercurrent events were premature discontinuation of treatment and use of rescue therapy for any reason. Intercurrent events are handled using the treatment policy strategy, i.e., data collected after the intercurrent event is continued to be used. In case of missing data in the data collected after the occurrence of intercurrent events, multiple imputation will be performed using the data of participants in the same treatment group (IBI362 group or placebo group) who have experienced intercurrent events but have collected the body weight measurement results at week 24. If an intercurrent event occurs but the model does not converge due to too little data collected from participants in the same treatment group with weight measurements at Week 24, multiple imputation will be performed using all data from participants in the same treatment group with weight measurements collected.

Imputation of missing values not due to intercurrent events:

For missing values not due to intercurrent events, multiple imputation will be performed using all data from the same group of participants with body weight measurements collected.

Sensitivity analysis:

- For missing data after the occurrence of intercurrent events, multiple imputation will be performed using the data of participants in the same group who have experienced the intercurrent event but have weight measurements collected at Week 24 (if the model does not converge due to too little data of participants in the same treatment group who have experienced the intercurrent event but have weight measurements collected at Week 24, multiple imputation will be performed using the data of all participants in the same group who have weight measurements collected); missing values not caused by the intercurrent event will be multiply imputed using J2R. That is, for participants who do not have intercurrent events but have missing weight measurements at Week 24, regardless of treatment group, the missing data will be multiply imputed using weight measurements collected from the placebo group.

- Missing data after intercurrent events and missing values not due to intercurrent events will be imputed using LOCF.
- Sensitivity analysis will be performed using the methods of RTD and tipping point, which will be described in detail in the SAP.

Supplementary analysis:

- Supplementary analysis was performed using the PPS.

Other sensitivity and supplementary analyses will be described in detail in the SAP.

Analyses Under the Efficacy Estimand

MMRM will be used, with treatment group, visit, treatment group-by-visit interaction, and randomization stratification factors as fixed categorical effects, and baseline body weight as the covariate. The corrected least squares estimates of the percentage change in body weight from baseline and their 95% CIs in the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group were calculated, respectively, and the inter-group difference estimates, corresponding standard errors, 95% CIs, and corresponding p-values of the two IBI362 dose groups vs. the placebo group were provided.

Intercurrent events and handling of intercurrent events:

Intercurrent events were premature discontinuation of treatment and use of rescue therapy for any reason. Data after the occurrence of an intercurrent event will not be included in the analysis, and the intercurrent event will be handled using a hypothetical strategy, assuming that no participants in the study experience drug efficacy in the event of an intercurrent event. Data after the occurrence of intercurrent events will be imputed using the MAR method built into the MMRM model SAS.

Imputation of missing values not due to intercurrent events:

Missing data not caused by intercurrent events will also be imputed using the MAR method built into the MMRM model of SAS.

Sensitivity and supplementary analyses will be described in detail in the SAP.

• Other Secondary Endpoints

For other secondary endpoints, it will be clearly specified in the SAP which secondary endpoints will be used for model fitting analysis under the treatment or efficacy estimand (the method is similar to that of the primary endpoint and major secondary endpoints), and which secondary endpoints will only be analyzed by descriptive statistics.

Sensitivity and supplementary analyses will be described in detail in the SAP.

The analysis of patient-reported outcome questionnaire scores will be detailed in the SAP.

8.5.3. Safety analysis

Unless otherwise specified, safety analysis will be performed in the SS.

8.5.3.1. Drug exposure

The drug exposure, duration of administration (weeks), and compliance of the participants during the study will be summarized.

8.5.3.2. Adverse event

The number and percentage of participants with each AE were summarized by system organ class, preferred term, and severity of adverse events in the Medical Dictionary for Regulatory Activities (MedDRA).

8.5.3.3. Laboratory tests

For blood routine, blood biochemistry, and other indicators, the measured values and changes before and after administration were described using mean $\pm$ standard deviation, maximum, minimum, and median by treatment group, and the normal and abnormal changes before and after administration were described using potentially clinically significant abnormalities (PCSAs) or cross-classification tables.

Normal and abnormal changes in urinalysis before and after treatment will be described using a cross-classification table.

8.5.3.4. 12-lead ECG

ECG measurements and changes were described. Normal and abnormal changes before and after treatment will be described using PCSA or cross-classification table.

8.5.3.5. Vital signs, physical examination, and other safety-related examinations

Vital signs at each visit will be summarized by group. Normal and abnormal changes before and after treatment will be described using PCSA or cross-classification table.

The proportion of "abnormal with clinical significance" in participants with abnormal changes in physical examination at each visit will be described by group. The clinical significance will be determined by Investigator.

8.5.3.6. Immunogenicity

Summarize and analyze the immunogenicity of IBI362.

8.5.3.7. Other safety measurements

Participants who died were listed in detail. Hypoglycemic events will be summarized by treatment group.

8.5.4. Pharmacokinetic analysis

The population PK characteristics of IBI362 will be analyzed using nonlinear mixed-

effect model.

8.5.5. Subgroup analyses

Subgroup analyses are planned to be performed on the stratification factors, i.e., HbA_{1c} level before randomization (V3) (<8.5% or ≥8.5%), and demographics and baseline characteristics such as age, gender, baseline weight, and baseline BMI. Will be defined in detail in the SAP.

8.5.6. Multiple comparisons and adjustments to multiplicity

Under each estimand, the statistical superiority of the two IBI362 dose groups over the placebo group in terms of the primary and major secondary endpoints will be adjusted for multiplicity using the sequential testing strategy. The order of testing is as follows:

- Change in HbA_{1c} from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Change in HbA_{1c} from baseline at week 24 (IBI362 4.0 mg vs. placebo);
- Proportion of participants with HbA_{1c} <7.0% at week 24 (IBI362 6.0 mg vs. placebo);
- Proportion of participants with HbA_{1c} <7.0% at week 24 (IBI362 4.0 mg vs. placebo);
- Proportion of participants with HbA_{1c} <7.0% and ≥5% weight reduction from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Proportion of participants with HbA_{1c} <7.0% and ≥5% weight reduction from baseline at week 24 (IBI362 4.0 mg vs. placebo);
- Proportion of participants with ≥5% weight loss from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Proportion of participants with ≥5% weight loss from baseline at week 24 (IBI362 4.0 mg vs. placebo);
- Percent change in body weight from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Percent change in body weight from baseline at week 24 (IBI362 4.0 mg vs. placebo).

The efficacy differences between each IBI362 dose group and the placebo group at each endpoint will be compared sequentially. If this endpoint is significant ($p < 0.05$), it can be considered that this IBI362 dose group is statistically superior to the placebo group at this endpoint, and the comparison of the next endpoint can be performed. If the comparison is not significant ($p \geq 0.05$), it is considered that the statistical superiority of IBI362 dose group over the placebo group on this endpoint is not established, and the

inter-group comparison on any endpoint after the endpoint sequence is not conducted.

All between-group comparisons were performed in parallel at the level of $\alpha = 0.05$ for both estimands. No multiplicity adjustment will be performed between the two estimands.

8.6. Control of bias

8.6.1. Randomization

Participants will be randomized in a 1:1:1 ratio to the IBI362 4.0 mg group, IBI362 6.0 mg group, or placebo group using block randomization. Randomization stratification factor is HbA_{1c} level before randomization (V3) (HbA_{1c} <8.5% or HbA_{1c} ≥8.5%).

Participant randomization will be completed using the IWRS. Participants who are successfully randomized will be assigned a randomization number and receive drug treatment according to the drug number assigned by the system. The unblinded statistician will complete the blinding of the randomization number and drug number of the participants and transmit them to the unblinded manager of the randomization system to complete the preparation and management of IWRS blinding.

The participants will be allocated by central randomization and enrolled competitively at all sites. The central randomization procedure will use a central randomization system. Participants who complete all screening assessments for this study and meet the inclusion criteria will receive a randomization number generated by the IWRS. This randomization number will connect the participants to the designated treatment group and can be assigned to the investigational product as needed. If a randomized participant withdraws from the study for any reason, the participant's randomization number will be retained. The IWRS staff will only be responsible for the configuration and management of the randomization system and will not participate in any specific trial operations.

8.6.2. Evaluation of maintenance of blinding

In this study, the participants and all investigators, monitors, sponsor personnel, and representatives involved in the treatment or clinical evaluation of the participants remained blinded until all participants completed the study and the database was locked.

8.6.3. Unblinding and emergency unblinding

During the clinical study, Investigator may perform emergency unblinding in the event of a medical emergency when he/she needs to know the study drug used by the participant for the safety of the participant. Before unblinding the investigational product, Investigator should first discuss with Sponsor's medical manager as much as possible. If this is not possible, the relevant personnel of Sponsor should be notified as soon as possible after emergency unblinding. Investigator should record the time of unblinding, the place of unblinding, and the reason for unblinding (the grouping information after

unblinding should not be recorded on the eCRF). In the case of emergency unblinding due to SAE, Investigator must complete the judgment of "relationship with the study drug" before performing emergency unblinding. The "relationship with the study drug" may not be revised based on the results of emergency unblinding. If unblinding occurs due to an emergency such as a serious adverse event, Investigator should explain the reason in writing to Sponsor, and the CRA should archive the written explanation.

9. Study Quality Assurance and Quality Control

According to the guidelines of Good Clinical Practice (GCP), Sponsor is responsible for implementing and maintaining quality assurance and quality control systems in accordance with the corresponding standard operating procedures to ensure that the implementation of the clinical trial and the collection, recording, and reporting of clinical trial data comply with the requirements of the protocol, GCP, and corresponding regulations.

9.1. Clinical monitoring

Sponsor or the CRO authorized by Sponsor will conduct clinical monitoring of this study. The CRA shall perform the monitoring in accordance with the standard operating procedures of Sponsor or CRO, and has the same rights and responsibilities as Sponsor's CRA. The CRA should maintain regular communication with Investigator and Sponsor.

Before the start of the study, the CRA will evaluate the qualifications of each study site and report issues related to facilities, technical equipment, or medical staff to Sponsor. During the study, the monitor will be responsible for monitoring whether the written informed consent has been obtained from all participants and whether the data records are correct and complete. Also, the monitor will compare the data entered into the eCRF with the source data, and inform Investigator of any errors or omissions. The CRA will also monitor the protocol compliance of the study site, arrange for the supply of the study drug, and ensure that the drug is kept under appropriate conditions.

The monitoring visit will be conducted in accordance with the requirements of relevant laws and regulations. Each site will receive regular monitoring visits from the time of participant enrollment. After each visit to Investigator, the CRA should submit a written report to Sponsor.

9.2. Data management

This study will use an electronic data capture (EDC) system, and the study data will be entered into the eCRF by Investigator or authorized study personnel. Before the initiation of the study site or data entry, Investigator and authorized study personnel will be properly trained, and appropriate security measures will be taken for the computers and other equipment used.

Data entry into the eCRFs should be completed as soon as possible during or after

visiting. The eCRFs should be updated at any time to ensure that they reflect the latest developments of the participants. To avoid differences in outcome evaluations by different evaluators, it is recommended that the baseline and all subsequent efficacy and safety evaluations of a given participant should be performed by the same evaluator. Investigator must review the data to ensure the accuracy and validity of all data entered into the eCRF. During the study, Investigator should document any evaluations that are not conducted, or any information that is not available, applicable, or known. Investigator should electronically sign the verified data.

The clinical research associate (CRA) will review the eCRF based on the source documents and assess the completeness and consistency. The CRA will compare the eCRF with the source documents to ensure the consistency of all data. All data entry, corrections, and modifications will be the responsibility of Investigator or his/her designee. The data in the eCRF will be submitted to the EDC database, and any changes to the data will be recorded in the audit trail, i.e., the reason for modification, the operator's user name, and the date and time of modification will be recorded. The roles and permissions of the personnel responsible for data entry at the study site will be predetermined. If there is any data query, the CRA or data manager will send a query in the EDC, and the relevant personnel of the study site will be responsible for answering the query. The EDC system will record the audit trail of the query, including user name, time, and date.

Unless otherwise specified, the eCRF will only be used as a form for collecting data, not as raw data. The source documents are used by Investigator or hospital, including all records related to the participants, which can prove the existence of the participants, the inclusion and exclusion criteria, and their participation in this study, including laboratory records, ECG results, medication records, and participant folders, etc.

Investigator is responsible for maintaining all source documents and providing them to the CRA for review during each visit. In addition, Investigator must submit a complete eCRF for each enrolled participant, regardless of the duration of study participation. The protocol number and participant number of all supporting documents (such as laboratory records or hospital records) submitted with the eCRF should be carefully verified, and all personal privacy information (including the participant's name) should be deleted or made illegible to protect the privacy of the participants. Investigator will certify by electronic signature that all eCRF data have been reviewed to ensure the validity, integrity, and accuracy of the data. The electronic signature will be completed using Investigator's user ID and password. The system will automatically attach the date and time of the signature. Investigator must not share his/her user ID and password with other personnel. If the data in the eCRF need to be modified, the procedures defined by the EDC system should be followed. All changes and reasons for the changes will be recorded in the audit trail.

9.3. Quality assurance audit

During the study, Sponsor or its authorized representative may conduct quality assurance audits on the study site, study database, and related study documents. At the same time, the corresponding regulatory authorities may also inspect the study site, study database, and related study documents at their own discretion. When Investigator receives an inspection notice from the regulatory authority, he/she must inform Sponsor immediately.

Sponsor's quality assurance department will conduct an audit of the clinical trial institution. The audit includes drug supply, required trial documents, documentation of the informed consent process, and consistency between case report forms and source documents. The content and scope of the audit can also be increased according to the situation. After reasonable notice, Investigator should allow auditors commissioned by Sponsor to conduct audits related to the trials and inspections conducted by the regulatory authorities. The primary purpose of an audit or an inspection is to verify that the rights or health of the participants have been protected, the signing of the informed consent form and the correct implementation of the trial process, and all data related to the evaluation of the study drugs have been processed, reported and pre-planned. In addition, the protocol, facility, ethical standard operating procedures, GCP and applicable regulatory requirements are consistent. Investigator should have direct access to all trial documents, source records, and source data.

10. Ethics

10.1. Ethics committee

Sponsor or Sponsor's authorized representative will prepare the relevant documents including the trial protocol, informed consent form, investigator's brochure, participant recruitment materials or advertisements, and other documents required by regulations, which are to be submitted to the Ethics Committee (EC) of the study site for approval. Prior to the start of the study, written approval from the EC must be obtained and submitted to Sponsor. The written approval from the EC must specify the name, number, version number of the study protocol, version number of other documents (such as ICF), and date of approval. Investigator is required to notify Sponsor of the EC's written comments on delay, suspension, and re-approval.

The study site must comply with the requirements of the EC of the site. Protocol amendments, ICF and recruitment materials should be submitted to the EC for approval. Local safety reports should be made and updated regularly in accordance with the regulations from the EC, and the final report should be submitted. All the above documents and EC approvals must be provided to Sponsor or its designated personnel.

10.2. Implementation of ethics

The study process and informed consent should be obtained in accordance with the Declaration of Helsinki, relevant GCP requirements, and laws and regulations related to drug and data protection in China.

GCP provides ethical and scientific global quality standards for the design, implementation, recording, and reporting of clinical studies involving human participants. This study will be conducted in accordance with GCP and relevant national regulations and in accordance with the relevant ethical principles of the Declaration of Helsinki to protect the rights, safety, and health of the participants.

Investigator must follow the procedures specified in this trial protocol and must not make changes without Sponsor's permission. Any protocol deviations will be reported to the EC, sponsor, or regulatory authorities.

10.3. Participant information and informed consent

Before the start of any study procedure, the ICF should be used to explain the risks and benefits of this study to potential participants, and the language used in the ICF should be simple and easy to understand. The ICF statement should clarify that the informed consent is voluntarily signed and the risks and benefits of participating in this study should be clearly outlined. The participant may withdraw from the study at any time. Investigator may only enroll a participant after fully explaining the details of the study, answering questions to the participant's satisfaction, giving the participant sufficient time for consideration, and obtaining written consent from the participant or his/her legal representative. All signed ICFs must be kept in Investigator's files or in the participant's folder.

Investigator is responsible for explaining the contents of the informed consent form to the participant and obtaining the informed consent form signed and dated by the participant or his/her legal representative before the start of the study. After signing, Investigator should provide the participant with a copy of the signed informed consent form. Investigator should document the informed consent process in the source document of the trial.

The initial informed consent form, any subsequent revisions of the written informed consent form, and any written information provided to the participants should have the opinion of the IRB/IEC before use. If new information becomes available that may be relevant to the participant's willingness to continue participation in the trial, the participant or his/her legal representative should be informed in a timely manner. This information will be provided and recorded in a revised informed consent form or an appendix to the original informed consent form (to obtain the participant's dated signature or the participant's legal representative's dated signature).

10.4. Data protection

Information on data protection and privacy protection will be included in the ICF (or in some cases, in a separate document).

Precautions should be taken to ensure the confidentiality of the documents and prevent the disclosure of information that can determine the identity of the participant. However, under special circumstances, some personnel may see a participant's genetic data and personal identification code. For example, in the event of a medical emergency, Sponsor, its representative physician, or Investigator will be aware of the participant identification code and have access to the participant's genetic data. In addition, relevant regulatory authorities require access to relevant documents.

10.5. Protocol deviation

A protocol deviation is any non-compliance with the clinical study protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or operating manual (MOP). The noncompliance may be either on the part of the participant, Investigator, or the study site personnel. For violations, corrective measures should be taken and completed in a timely manner.

11. Study Management

11.1. Data processing and record keeping

Clinical trial documents (protocol and protocol amendments, completed eCRFs, signed ICFs, etc.) should be stored and managed in accordance with the GCP. The study site should keep these documents for 5 years after the clinical trial drug is marketed.

The study documents should be reasonably kept for future access or data traceability. Security and environmental risks should be considered when storing documents.

No study documents should be destroyed without the written permission of Sponsor and investigator. Investigator/study site may transfer the study documents to other parties that comply with the document retention requirements or transfer the documents to other locations that meet the requirements only after notifying Sponsor and obtaining its written consent.

11.2. Source data/document access

Investigator agrees that Sponsor, CRO, and relevant authorized regulatory authorities will have direct access to all study-related documents, including medical records of participants.

11.3. Protocol amendments

All amendments to the protocol during the study must be communicated between and agreed by Sponsor and Investigator. Sponsor should ensure that protocol amendments are submitted to the regulatory authorities in a timely manner.

All revisions to the protocol should be kept as protocol supplements. Any amendments to the protocol must be submitted to the Ethics Committee for approval or filing in accordance with the regulations of the Ethics Committee. If necessary, it should also be submitted to regulatory authorities for approval and only implemented after being approved by the EC and regulatory authorities (if applicable) (with the exception of changes to the protocol that eliminate direct hazards to the trial participants).

11.4. Investigator responsibilities

Investigator will carry out this study in accordance with the protocol, ethical principles of the Declaration of Helsinki, Chinese GCP, and corresponding regulatory requirements.

The detailed responsibilities of relevant investigators are listed in Chapter 5 of China GCP (No. 57 of 2020).

11.5. Publication policy

All data generated in this study are confidential information owned by Sponsor, and Sponsor has the right to publish the study results. Information on the publication policies of Sponsor and Investigator will be described in the clinical trial agreement.

All information related to this trial (not limited to the protocol and Investigator's Brochure) must be kept strictly confidential. Investigator must recognize that the scientific or medical conclusions drawn from this trial may be of commercial value to Sponsor. Investigator should keep the information and data related to this trial confidential. If Investigator wants to publish the data related to this trial or the conclusions drawn from the trial, he/she must consult with Sponsor in advance and obtain the written consent of Sponsor. In order to protect its rights, Sponsor may request Investigator not to publish relevant trial data before the investigational product is approved for marketing.

Sponsor has the right to publish or release the information or data related to this trial or to report it to the drug administration. If Sponsor needs to display the name of Investigator in the content published, released, or advertised, the consent of Investigator should be obtained.

11.6. Financing and insurance

Sponsor will purchase insurance for participants participating in this study in accordance with local regulations and minimum requirements. The relevant insurance clauses will be kept in the study folder.

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13. Appendices

Appendix 1. Protocol Revision History

Attached Table 1. Protocol revision history

Version	Date
V1.0	Feb. 25, 2022
V2.0	Sep. 15, 2022
V3.0	Jan. 31, 2023
V4.0	Mar. 14, 2024

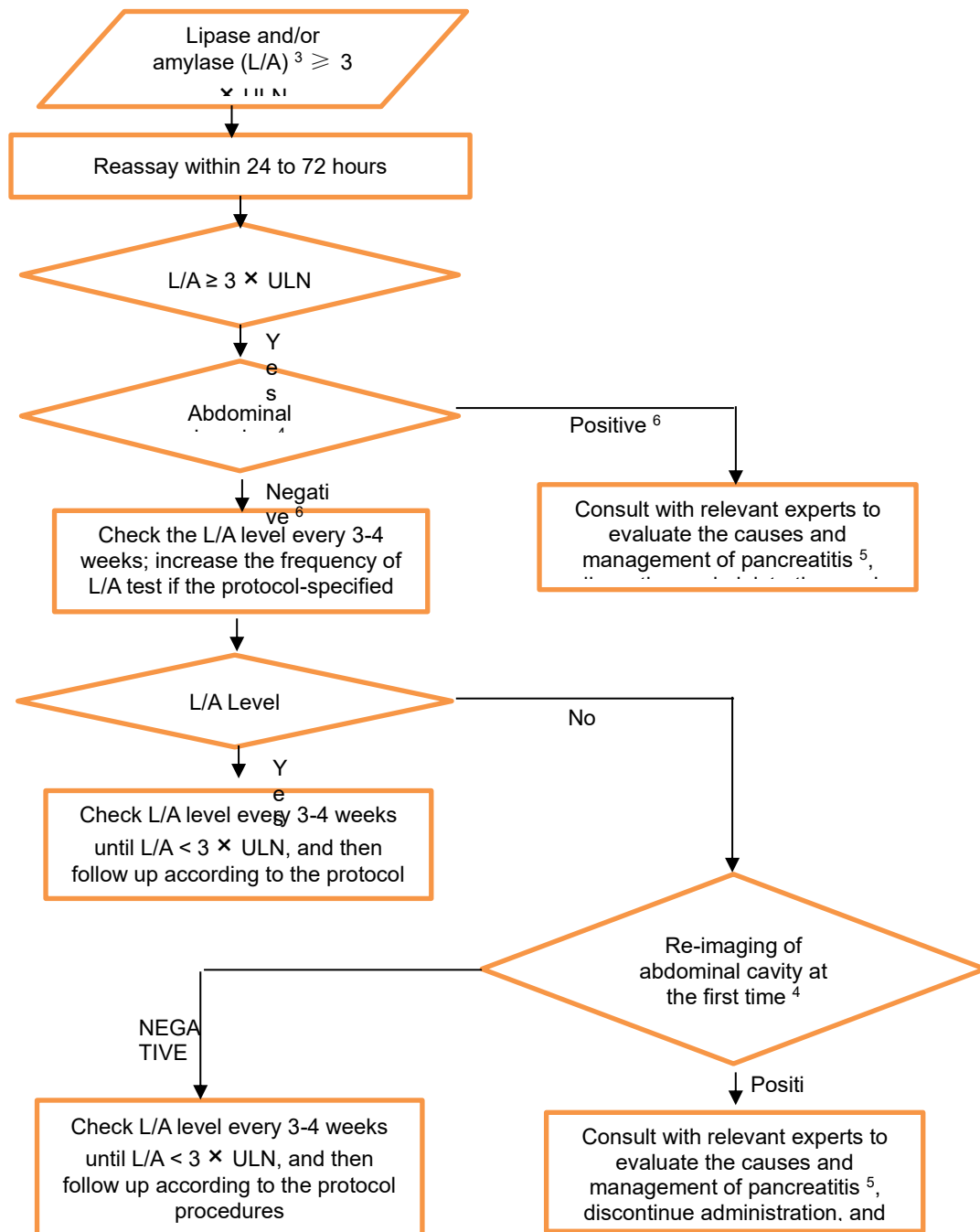
Appendix 2. CKD-EPI equation (eGFR estimation equation)

CKD-EPI estimation formula:

Gender	Serum creatinine (Scr)	Calculation formula of eGFR
Female	$\leq 62 \mu\text{mol/L}$ ($\leq 0.7 \text{mg/dl}$)	$\text{GFR} = 144 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{age}}$
	$> 62 \mu\text{mol/L}$ ($> 0.7 \text{mg/dl}$)	$\text{GFR} = 144 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{age}}$
Male	$\leq 80 \mu\text{mol/L}$ ($\leq 0.9 \text{mg/dl}$)	$\text{GFR} = 141 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{age}}$
	$> 80 \mu\text{mol/L}$ ($> 0.9 \text{mg/dl}$)	$\text{GFR} = 141 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{age}}$

Reference: Levey AS, et. al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009.

Appendix 3. Algorithm for monitoring and management of pancreatic enzymes in patients without symptoms of pancreatitis ^{1,2}



1. Symptoms mainly refer to pancreatitis-related abdominal pain, severe nausea, vomiting, and other symptoms that can also be considered as related symptoms by Investigator.
2. If Investigator believes that the participant has symptoms of acute pancreatitis at any time, regardless of whether it is based on L/A test results, he/she should consult an expert for evaluation and management, evaluate the cause of pancreatitis, discontinue the drug administration, and notify Sponsor.
3. Either or both of blood lipase and blood amylase may be used as evaluation criteria.
4. The best time to image the abdomen is when pancreatic enzymes are first noted to be elevated. If Investigator or radiologist judges that it is safe, it is best to use enhanced abdominal CT for examination, and MRI is also acceptable.
5. At least liver function parameters, triglycerides, and blood calcium levels should be examined,

- and all concomitant medications should be recorded.
6. Negative and positive imaging findings are specific to acute pancreatitis.

Appendix 4. Judgment of causality between adverse events and study drugs

Relationship to Sponsor's Product	Is the AE caused by the study drug? A medically qualified investigator is required to provide a causality assessment between the study drug and the AE. Investigator will sign/date (initials) the source document or worksheet to support the causality assessment on the AE form to ensure a medically qualified causality assessment. This signed document must be retained for the required regulatory time frame. The following criteria are intended to serve as a reference guide to assist Investigator in evaluating the relationship between the study drug and AEs based on available information. The following elements are used to assess the relationship between the study drug and AEs; The greater the correlation between each item and their corresponding elements (in terms of quantity and/or intensity), the greater the possibility that the study drug causes AEs;	
	Exposure	Is there any evidence that the participant is indeed exposed to the study drug, such as: authentic and credible medical history, acceptable compliance assessment (drug count, diary, etc.), expected pharmacological effect, and measurement of drug/metabolites in in vivo samples collected?
	Time course	Is there a reasonable temporal sequence between the adverse event and the trial drug treatment? Does the onset time of the adverse event meet the criteria for drug-induced adverse events?
	Reasons other than the study drug	Whether there are other etiological explanations for the AE, such as underlying disease, other drugs/vaccines, or other host or environmental factors
	Dechallenge	Was study drug discontinued or dose/exposure/frequency reduced? If yes, can the AE be resolved or improved? If Yes, Dechallenge was Positive. If none, it indicates a negative dechallenge. Note: This criterion is not applicable if the following occurs: (1) the AE results in death or permanent disability; (2) the AE resolves/improves despite continuing treatment with the study drug; (3) the study is a single-dose study; (4) only one dose of the study drug is administered.

	Rechallenge	Was the participant repeatedly exposed to the study drug in this trial? If yes, can the AE reoccur or worsen? If yes, positive rechallenge. If not, the rechallenge is negative. Note: This criterion does not apply if: (1) the initial AE results in death or permanent disability, (2) the trial is a single-dose clinical trial, or (3) only one dose of the study drug is used. Note: If a rechallenge is planned for an AE that is serious and may be caused by the study drug, or if re-exposure to the study drug may result in serious potential risks to the participant, a rechallenge is not recommended in this case, unless it is considered that continued medication may be beneficial to the participant and there is no alternative treatment available, and the rechallenge can be performed after Sponsor's approval is obtained in advance.
	Consistency with trial treatment characteristics	Are the clinical/pathological manifestations of the adverse event consistent with the data of previous pharmacological and toxicological studies of the study drug or such drugs?
Investigator with medical qualifications will record the causality assessment results based on his/her best clinical judgment, including consideration of the above causality assessment factors. The assessment result of the causal relationship between an adverse event and the study drug will be recorded as "related" and "not related".		
Documenting Causality	The following table can be used for causality assessment (not all criteria need to be met)	
Related	There is generally evidence of exposure to the study drug. A reasonable time sequence between the occurrence of the AE and the administration of Sponsor's product. The occurrence of the AE is more likely explained by the study drug than by other causes.	
Not related	It generally refers to that the participant does not use the study drug, the time management of the occurrence of adverse event and the occurrence of adverse event is unreasonable, or there are other reasons that can explain the adverse event better, rather than the study drug.	

Appendix 5. Fasting Body Weight Measurement SOP

Body weight should be measured in a uniform manner using a calibrated scale (either mechanical or electronic) at each visit for each participant. When measuring weight, participants should take off coats/trousers/hats/scarves/necklaces/belts and other clothing that increase weight, wear only single clothes (only one top and one bottom), and take off shoes. Make sure the scale is zeroed before weighing.

Before weighing, make sure that the scale is placed on a smooth surface (not on a carpet or on an inclined surface or a rough surface).

1. Before weighing, the curtain should be pulled to isolate the weighing area to protect the privacy of the participant when changing clothes.
2. Before weighing, make sure that the participant does not feel cold after undressing.
3. After verifying whether the participant has urinated, guide the participant into the weighing area, pull up the curtain, ask the participant to take off coats/outer pants/hats/scarves/necklaces/belts and other clothing that increase weight, only wear single clothes (only one top and one bottom), and take off shoes.
4. Participants are required to step on the scale with their feet placed on each side of the scale.
5. Participants are required to stand still with their arms at their sides and then record their weight to 1 decimal place in kilograms (kg).

Appendix 6. Diagnosis of type 2 diabetes: 1999 WHO criteria (supplementary version) ^[1]

Diagnostic criteria	Venous plasma glucose* or HbA1c levels
Typical symptoms of diabetes	
Plus random glucose	≥ 11.1 mmol/L
or plus fasting glucose	≥ 7.0 mmol/L
Or add OGTT 2h blood glucose	≥ 11.1 mmol/L
or plus HbA1c	$\geq 6.5\%$
Those without typical symptoms of diabetes need to be rechecked another day for confirmation	

Note: * This item was not available in the local laboratory and could be replaced by fasting serum glucose. OGTT is oral glucose tolerance test; hbA1c is glycosylated hemoglobin. Typical symptoms of diabetes include polydipsia, polyuria, polyphagia, and unexplained weight loss; random blood glucose refers to blood glucose at any time of the day regardless of the time of the last meal, which cannot be used to diagnose impaired fasting blood glucose or abnormal glucose tolerance; fasting state refers to no calorie intake for at least 8 h.

In order to be in line with the WHO diagnostic criteria, it is recommended that $\text{HbA1c} \geq 6.5\%$ can be used as a supplementary diagnostic criterion for diabetes in medical institutions that use standardized testing methods and have strict quality control (National Glycosylated Hemoglobin Standardization Plan, Chinese Glycosylated Hemoglobin Consistency Research Plan). However, diabetes can only be diagnosed based on venous plasma glucose levels in the following situations: sickle cell disease, pregnancy (intermediate and late stages), glucose-6-phosphate dehydrogenase deficiency, AIDS, hemodialysis, recent blood loss or transfusion, erythropoietin treatment, etc. In addition, screening for cystic fibrosis-related diabetes with hemoglobin A1c is not recommended.

REFERENCES:

[1] Chinese Diabetes Society. Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition) [J]. Chinese Journal of Diabetes Mellitus, 2021, 13(4): 317-411.