
Supplementary information

Mazdutide versus placebo in Chinese adults with type 2 diabetes

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Mazdutide versus placebo in Chinese adults with type 2 diabetes

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Supplementary Information

Inclusion and Exclusion Criteria of the DREAMS-1 Trial

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.
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 $\geq 23 \text{ kg/m}^2$ at screening.
5. Able to maintain a stable diet and exercise lifestyle during the study.
6. Participants who voluntarily sign the ICF and agree to strictly follow the requirements of this protocol.

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 $>3.0 \times$ ULN (ALT $>5.0 \times$ ULN for non-alcoholic fatty liver disease), or AST $>3.0 \times$ ULN, or total bilirubin (TBIL) $>2.0 \times$ 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 participant 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.
- 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.

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.

List of Investigators In the DREAMS-1 Trial

Study Site	Investigator	Participant s screened	Enrollment failed	Lead-in failed	Participants enrolled
Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China	Dalong Zhu	7	3	0	4
Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China	Jiajun Zhao	17	5	3	9
The Second Hospital of Jilin University, Changchun, China	Hanqing Cai	20	2	2	16
The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China	Xuan Chu	22	6	1	15
Xuanwu Hospital Capital Medical University, Beijing, China	Shuangling Xiu	28	12	2	14
Jilin Province FAW General Hospital, Changchun, China	Chengwei Song	21	5	3	13
The Fourth Affiliated Hospital, Harbin Medical University, Harbin, China	Zhifeng Cheng	20	8	0	12
Chengdu Fifth People's Hospital, Chengdu, China	Hongyi Cao	18	6	0	12
The First Affiliated Hospital of Henan University of Science & Technology, Luoyang, China	Hongwei Jiang	18	6	1	11
Jincheng General Hospital, Jincheng, China	Lili Zhang	12	1	0	11
Handan First Hospital, Handan, China	Haifang Wang	15	4	0	11
The First Affiliated Hospital of Soochow University, Suzhou, China	Bimin Shi	15	5	0	10
The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China	Yanbing Li	2	1	0	1
Tianjin Medical University General Hospital, Tianjin, China	Ming Liu	12	6	1	5
Shanghai East Hospital, Tongji University, Shanghai, China	Bo Feng	7	2	1	4
Beihua University Affiliated Hospital, Jilin, China	Yushan Guo	19	6	4	9
Jinan Central Hospital, Jinan, China	Xiaolin Dong	12	3	0	9
The Affiliated Sir Run Run Shaw Hospital of Nanjing Medical University, Nanjing, China	Yu Liu	16	6	1	9
Yuncheng Central Hospital, Yuncheng, China	Xiaojing Wang	14	5	0	9
Nanjing Jiangning Hospital, Nanjing, China	Kun Wang	13	4	1	8

Huadong Hospital, Shanghai, China	Jiao Sun	13	4	1	8
Kunshan First People's Hospital, Kunshan, China	Shao Zhong	7	0	0	7
Changde First People's Hospital, Changde, China	Haifeng Zhou	14	7	0	7
Pingxiang People's Hospital, Pingxiang, China	Yawei Zhang	15	5	3	7
The First Affiliated Hospital of Nanyang Medical College, Nanyang, China	Dexue Liu	11	4	0	7
Shanghai Tongren Hospital, Shanghai, China	Shanhuang	13	5	1	7
The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China	Yibing Lu	6	0	0	6
CNPC Central Hospital Hebei, Langfang, China	Jie Han	15	6	3	6
Zhengzhou People's Hospital	Qijuan Dong	7	1	0	6
Heilongjiang Provincial Hospital, Harbin, China	Binhong Duan	12	5	2	5
The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China	Suhe Zhang	9	4	0	5
Panjin Liaohe Oilfield Baoshihua Hospital, Panjin, China	Xin Zhang	12	6	1	5
Ningbo First Hospital, Ningbo, China	Jialin Li	6	1	0	5
Cangzhou Hospital of Integrated Chinese and Western Medicine, Hebei Province, Cangzhou, China	Xiaoyun Wang	7	1	1	5
Jining First People's Hospital, Jining, China	Feng Li	7	1	1	5
The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, China	Guoqing Ma	10	5	1	4
Huai'an First People's Hospital, Huai'an, China	Li Mao	8	4	0	4
Harrison International Peace Hospital, Hengshui, China	Jianlin Geng	7	2	1	4
Chenzhou First People's Hospital, Chenzhou, China	Weihong Song	5	2	0	3
Huzhou Central Hospital, Huzhou, China	Wei Qiu	4	1	0	3
Xiangtan First People's Hospital, Xiangtan, China	Genqing Xie	10	4	3	3
The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China	Xingxing Zhang	9	4	2	3
Pinggu District Hospital, Beijing, China	Yufeng Li	6	2	1	3

The First Hospital of Lanzhou University, Lanzhou, China	Chengdong Qiao	4	0	2	2
The Affiliated Three Gorges Hospital of Chongqing University, Chongqing, China	Cheng Zhang	5	2	1	2
The Second Hospital of Shanxi Medical University, Taiyuan, China	朱亦堃	6	2	2	2
Pudong New Area People's Hospital, Shanghai, China	Xiaozhen Jiang	3	1	0	2
Liuzhou Workers' Hospital, Liuzhou, China	Tingting Deng	12	8	3	1
Taian Central Hospital, Taian, China	Tie Zhang	5	4	1	0

List of Ethics Committees Approving the DREAMS-1 Trial

Study Site	Ethic Committee
Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China	Medical Ethics Committee of Nanjing Drum Tower Hospital Affiliated to the Medical School of Nanjing University
Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China	Ethics Committee for Drug Clinical Trials of Shandong Provincial Hospital
The Second Hospital of Jilin University, Changchun, China	Medical Ethics Committee of the Second Hospital of Jilin University
The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China	Medical Ethics Committee of the Affiliated Hospital of Xuzhou Medical University
Xuanwu Hospital Capital Medical University, Beijing, China	Ethics Committee of Xuanwu Hospital, Capital Medical University
Jilin Province FAW General Hospital, Changchun, China	Ethics Committee for Drug/Device Clinical Trials of FAW General Hospital
The Fourth Affiliated Hospital, Harbin Medical University, Harbin, China	Clinical Trial Ethics Committee of the Fourth Affiliated Hospital of Harbin Medical University
Chengdu Fifth People's Hospital, Chengdu, China	Ethics Committee of Chengdu Fifth People's Hospital
The First Affiliated Hospital of Henan University of Science & Technology, Luoyang, China	Medical Ethics Committee of the First Affiliated Hospital of Henan University of Science and Technology
Jincheng General Hospital, Jincheng, China	Clinical Trial Sub - Committee of Ethics Committee of Jincheng Grand Hospital
Handan First Hospital, Handan, China	Ethics Committee for Clinical Trials of Handan First Hospital, Hebei Province
The First Affiliated Hospital of Soochow University, Suzhou, China	Medical Ethics Committee of the First Affiliated Hospital of Soochow University
The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China	Ethics Committee for Clinical Drugs, Equipment and New Medical Technologies of The First Affiliated Hospital of Sun Yat-sen University
Tianjin Medical University General Hospital, Tianjin, China	Drug Ethics Committee of General Hospital of Tianjin Medical University
Shanghai East Hospital, Tongji University, Shanghai, China	Medical Ethics Committee of Shanghai East Hospital (East Hospital Affiliated to Tongji University)

Beihua University Affiliated Hospital, Jilin, China	National Ethics Committee for Drug Clinical Trials of the Affiliated Hospital of Beihua University
Jinan Central Hospital, Jinan, China	Medical Ethics Committee of Jinan Central Hospital
The Affiliated Sir Run Run Shaw Hospital of Nanjing Medical University, Nanjing, China	Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Nanjing Medical University
Yuncheng Central Hospital, Yuncheng, China	Ethics Committee of Yuncheng Central Hospital, Shanxi Province
Nanjing Jiangning Hospital, Nanjing, China	Ethics Committee of Nanjing Jiangning Hospital
Huadong Hospital, Shanghai, China	Ethics Committee of Huadong Hospital Affiliated to Fudan University
Kunshan First People's Hospital, Kunshan, China	Medical Ethics Committee of Kunshan First People's Hospital
Changde First People's Hospital, Changde, China	Ethics Committee for Drug Clinical Trials of Changde First People's Hospital
Pingxiang People's Hospital, Pingxiang, China	Ethics Committee of Pingxiang People's Hospital
The First Affiliated Hospital of Nanyang Medical College, Nanyang, China	Clinical Trial Ethics Committee of the First Affiliated Hospital of Nanyang Medical College
Shanghai Tongren Hospital, Shanghai, China	Ethics Committee of Shanghai Tongren Hospital
The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China	Medical Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University
CNPC Central Hospital Hebei, Langfang, China	Clinical Trial Ethics Committee of CNPC Hebei Central Hospital
Zhengzhou People's Hospital	Ethics Committee for Drug Clinical Trials of Zhengzhou People's Hospital
Heilongjiang Provincial Hospital, Harbin, China	Clinical Trial Ethics Committee of Heilongjiang Provincial Hospital
The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China	Clinical Trial Ethics Committee of the Second Affiliated Hospital of Zhengzhou University
Panjin Liaohe Oilfield Baoshihua Hospital, Panjin, China	Panjin Liaoyou Baoshihua Hospital Clinical Research Ethics Committee
Ningbo First Hospital, Ningbo, China	Ethics Committee for Drug and Device Clinical Trials of the First Affiliated Hospital of Ningbo University
Cangzhou Hospital of Integrated Chinese and Western Medicine, Hebei Province, Cangzhou, China	Ethics Committee for Clinical Trials of Cangzhou Hospital of Integrated Chinese and Western Medicine, Hebei Province
Jining First People's Hospital, Jining, China	Medical Ethics Committee of Jining First People's Hospital

The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, China	Clinical Trial Ethics Review Committee of the Second Affiliated Hospital of Heilongjiang University of Chinese Medicine
Huai'an First People's Hospital, Huai'an, China	Medical Ethics Committee of Huai'an First People's Hospital
Harrison International Peace Hospital, Hengshui, China	Ethics Committee for Clinical Trials of Drugs (Medical Devices) of Harrison International Peace Hospital
Chenzhou First People's Hospital, Chenzhou, China	Ethics Committee of Chenzhou First People's Hospital
Huzhou Central Hospital, Huzhou, China	Clinical Trial Ethics Committee of Huzhou Central Hospital
Xiangtan First People's Hospital, Xiangtan, China	Ethics Committee of Xiangtan First People's Hospital
The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China	Ethics Committee for Drug Clinical Trials of the First Affiliated Hospital of Wenzhou Medical University
Pinggu District Hospital, Beijing, China	Medical Ethics Committee of Pinggu District Hospital, Beijing
The First Hospital of Lanzhou University, Lanzhou, China	Medical Ethics Committee of the First Hospital of Lanzhou University
The Affiliated Three Gorges Hospital of Chongqing University, Chongqing, China	Ethics Committee for Drug Clinical Trials of Three Gorges Hospital Affiliated to Chongqing University
The Second Hospital of Shanxi Medical University, Taiyuan, China	Ethics Committee of the Second Hospital of Shanxi Medical University
Pudong New Area People's Hospital, Shanghai, China	Ethics Committee for Clinical Trials of Shanghai Pudong New Area People's Hospital
Liuzhou Workers' Hospital, Liuzhou, China	Ethics Committee of Liuzhou Worker's Hospital
Taian Central Hospital, Taian, China	Clinical Trial Ethics Committee of Taian Central Hospital

Supplementary Table 1. Glycemic and body weight efficacy outcomes at week 24 reported under the efficacy estimand

	Mazdutide 4 mg (N=106)		Mazdutide 6 mg (N=106)		Placebo (N=107)
	Mean	p	Mean	p	Mean
HbA_{1c}, %					
No. of participants with HbA_{1c} measures at week 24	n=89		n=85		n=82
Change from baseline, %	-1.57 (0.107)		-2.15 (0.109)		-0.14 (0.107)
versus placebo	-1.43 (-1.73, -1.13)	<0.0001	-2.02 (-2.32, -1.72)	<0.0001	
Change from baseline, mmol/mol	-17.11 (1.171)		-23.54 (1.192)		-1.48 (1.165)
versus placebo	-15.63 (-18.88, -12.37)	<0.0001	-22.06 (-25.34, -18.77)	<0.0001	
Participants with HbA_{1c} <7.0%, %	68.6 (59.2, 78.0)		87.4 (80.6, 94.2)		10.7 (4.7, 16.7)
versus placebo	57.0 (46.1, 67.8)	<0.0001	76.2 (67.2, 85.2)	<0.0001	
Participants with HbA_{1c} ≤6.5%, %	55.6 (45.6, 65.6)		81.5 (73.4, 89.7)		4.4 (0.4, 8.5)
versus placebo	50.7 (39.8, 61.5)	<0.0001	76.9 (67.8, 85.9)	<0.0001	
Participants with HbA_{1c} <5.7%, %	11.7 (5.0, 18.4)		27.4 (17.7, 37.0)		0 (0.0, 3.4)
versus placebo	11.3 (4.7, 17.9)	0.0262	26.7 (17.2, 36.2)	0.0030	
FPG, mmol/L					
No. of participants with FPG measures at week 24	n=89		n=86		n=82
Change from baseline, mmol/L	-2.43 (0.190)		-3.28 (0.193)		0.22 (0.192)
versus placebo	-2.65 (-3.18, -2.11)	<0.0001	-3.50 (-4.03, -2.96)	<0.0001	
Daily mean SMBG, mmol/L					
No. of participants with daily mean SMBG measures at week 24	n=88		n=83		n=78
Change from baseline, mmol/L	-3.82 (0.187)		-4.41 (0.190)		-1.45 (0.191)
versus placebo	-2.37 (-2.89, -1.85)	<0.0001	-2.96 (-3.49, -2.44)	<0.0001	
Body weight, kg					
No. of participants with body weight measures at week 24	n=89		n=86		n=82
Percent change from baseline, %	-5.61 (0.459)		-7.81 (0.466)		-1.26 (0.459)
versus placebo	-4.35 (-5.63, -3.07)	<0.0001	-6.55 (-7.84, -5.26)	<0.0001	
Change from baseline, kg	-4.28 (0.350)		-5.82 (0.355)		-0.97 (0.350)
versus placebo	-3.31 (-4.29, -2.34)	<0.0001	-4.85 (-5.83, -3.87)	<0.0001	
Participants with ≥5% weight loss, %	50.9 (40.6, 61.3)		69.0 (59.6, 78.4)		7.3 (1.6, 13.1)
versus placebo	43.5 (31.8, 55.2)	<0.0001	60.8 (49.8, 71.8)	<0.0001	
Participants with ≥10% weight loss, %	19.2 (11.1, 27.2)		34.7 (25.1, 44.3)		0 (0.0, 3.4)
versus placebo	19.0 (11.0, 26.9)	0.0094	32.9 (23.7, 42.1)	0.0017	
Participants with ≥5% weight loss and HbA_{1c} <7.0%, %	40.6 (30.7, 50.5)		64.9 (55.2, 74.6)		0 (0.0, 3.4)

	Mazdutide 4 mg (N=106)		Mazdutide 6 mg (N=106)		Placebo (N=107)
	Mean	<i>p</i>	Mean	<i>p</i>	Mean
versus placebo	39.8 (30.1, 49.4)	0.0008	63.3 (53.9, 72.6)	<0.0001	

For continuous outcomes, data are LS means (SE or 95% CI), from an MMRM analysis, mITT population. For binary outcomes, missing data are imputed by MI assuming missing at random and then the binary outcomes are dichotomized from the corresponding continuous variables. Data are percentages and 95% CI calculated by combining the percentages of participants who met the goals in imputed data sets using Rubin's rules, from logistic regression analysis, mITT population. Estimated treatment differences are LS means (95% CI). All *p* values were two-sided. LS=least squares. mITT=modified intent-to-treat. MI: multiple imputation. SMBG=self-measured blood glucose. SE=standard error. CI=confidence interval. FPG=fasting plasma glucose. HbA_{1c}=glycated hemoglobin A1c. LS=least squares. MMRM=mixed model repeated measures. MI=multiple imputation.

Supplementary Table 2: Sensitivity analyses of the change in HbA_{1c} and body weight at week 24 reported under the treatment-policy estimand

	Mazdutide 4 mg (N=106)		Mazdutide 6 mg (N=106)		Placebo (N=107)
	Mean	<i>p</i>	Mean	<i>p</i>	Mean
Change in HbA_{1c} †††					
Main analysis [#]					
Change from baseline, %	-1.58 (0.091)		-2.02 (0.089)		-0.25 (0.087)
Treatment difference vs placebo	-1.33 (-1.57, -1.08)	<0.0001	-1.77 (-2.01, -1.53)	<0.0001	
Sensitivity analysis 1 *					
Change from baseline, %	-1.58 (0.091)		-2.01 (0.089)		-0.26 (0.088)
Treatment difference vs placebo	-1.32 (-1.57, -1.07)	<0.0001	-1.75 (-1.99, -1.51)	<0.0001	
Sensitivity analysis 2 (LOCF)					
Change from baseline, %	-1.48 (0.087)		-1.93 (0.087)		-0.24 (0.087)
Treatment difference vs placebo	-1.23 (-1.47, -0.99)	<0.0001	-1.68 (-1.92, -1.44)	<0.0001	
Sensitivity analysis 3 (R2B)					
Change from baseline, %	-1.38 (0.101)		-1.82 (0.103)		-0.25 (0.100)
Treatment difference vs placebo	-1.13 (-1.41, -0.85)	<0.0001	-1.57 (-1.85, -1.29)	<0.0001	
Percentage change in body weight, % †††					
Main analysis [#]					
Percentage change from baseline, %	-5.50 (0.504)		-7.34 (0.492)		-1.15 (0.467)
Treatment difference vs placebo	-4.34 (-5.69, -3.00)	<0.0001	-6.18 (-7.51, -4.85)	<0.0001	
Sensitivity analysis 1 *					
Percentage change from baseline, %	-5.44 (0.508)		-7.34 (0.494)		-1.16 (0.468)
Treatment difference vs placebo	-4.28 (-5.63, -2.92)	<0.0001	-6.18 (-7.51, -4.84)	<0.0001	
Sensitivity analysis 2 (LOCF)					
Percentage change from baseline, %	-5.11 (0.450)		-6.80 (0.451)		-1.14 (0.448)
Treatment difference vs placebo	-3.96 (-5.21, -2.71)	<0.0001	-5.65 (-6.90, -4.40)	<0.0001	
Sensitivity analysis 3 (R2B)					
Percentage change from baseline, %	-4.80 (0.506)		-6.30 (0.509)		-1.11 (0.488)
Treatment difference vs placebo	-3.69 (-5.07, -2.31)	<0.0001	-5.19 (-6.57, -3.81)	<0.0001	

Data are LS mean and its difference (95% CI). For continuous endpoints, analysis of covariance (ANCOVA) was used and for binary endpoints, the logistic regression model was used. The treatment group and the stratification factor were as fixed effects in the model, and the baseline HbA_{1c} or body weight as covariate. All *p* values were two-sided.

[#]For missing data happened after early discontinuation of study treatment and initiation of rescue therapy, multiple imputation was pre-specified to use the data of the same group of participants who occurred the intercurrent event but whose corresponding measurements were collected, if model were not converges, the data of all the participants from the same group would be used for imputation; For missing data not due to the two intercurrent events mentioned above, multiple imputation was performed using the placebo group of participants who collected the corresponding outcome measurements.

††† $p < 0.0001$ for superiority comparison versus placebo.

LOCF denotes the last observation carried forward, and R2B denotes return to baseline.

A tipping point analysis was also conducted for the primary endpoint between mazdutide 4 mg or 6mg versus placebo in Change in HbA_{1c}. For both treatments of mazdutide 4 mg or 6mg, no penalty could be added to reverse the conclusion of main analysis in the range explored (from 0.1% to 1.0% by 0.1% in the mazdutide groups and at the same time from -0.1% to -1.0% by -0.1% in the placebo group).

LS= least squares. CI=confidence interval. HbA_{1c}=glycated hemoglobin A_{1c}

Supplementary Table 3. Other efficacy outcomes at week 24 reported under the treatment-policy estimand

	Mazdutide 4 mg (N=106)		Mazdutide 6 mg (N=106)		Placebo (N=107)
	Mean	P	Mean	P	Mean
1,5-Anhydroglucitol, µg/ml					
Baseline, µg/ml	4.8 (4.6)		3.9 (3.4)		4.0 (3.5)
Change from baseline, µg/ml	8.6 (0.6)		9.8 (0.6)		1.4 (0.6)
versus placebo	7.2 (5.6, 8.8)	<0.0001	8.4 (6.8, 10.0)	<0.0001	
Waist circumference, cm					
Baseline, cm	97.72 (11.483)		96.25 (10.688)		98.19 (10.444)
Change from baseline, cm	-3.66 (0.398)		-4.42 (0.392)		-0.43 (0.378)
versus placebo	-3.23 (-4.31, -2.15)	<0.0001	-3.99 (-5.05, -2.92)	<0.0001	
BMI, kg/m²					
Baseline, kg/m ²	28.25 (3.973)		27.80 (3.794)		28.60 (3.983)
Change from baseline, kg/m ²	-1.52 (0.136)		-2.04 (0.135)		-0.32 (0.130)
versus placebo	-1.20 (-1.57, -0.83)	<0.0001	-1.73 (-2.09, -1.36)	<0.0001	
Systolic blood pressure, mm Hg					
Baseline, mm Hg	125.307 (11.6529)		124.748 (12.3997)		127.072 (11.9593)
Change from baseline, mm Hg	-7.10 (1.056)		-6.02 (1.089)		-2.25 (1.018)
versus placebo	-4.85 (-7.73, -1.96)	0.0010	-3.77 (-6.67, -0.86)	0.0111	
Diastolic blood pressure, mm Hg					
Baseline, mm Hg	82.119 (7.8124)		82.075 (7.6790)		82.903 (6.5736)
Change from baseline, mm Hg	-2.20 (0.708)		-2.29 (0.735)		0.09 (0.678)
versus placebo	-2.30 (-4.23, -0.37)	0.0197	-2.38 (-4.32, -0.45)	0.0160	
Total cholesterol, mmol/L					
Baseline, mmol/L	4.88 (1.004)		4.94 (1.125)		4.97 (1.049)
Change from baseline, mmol/L	-0.61 (0.077)		-0.69 (0.077)		-0.10 (0.075)
versus placebo	-0.51 (-0.72, -0.30)	<0.0001	-0.59 (-0.80, -0.38)	<0.0001	
Percent change from baseline, %	-10.89 (1.569)		-11.74 (1.546)		-0.45 (1.507)
versus placebo	-10.44(-14.68, -6.21)	<0.0001	-11.29 (-15.51, -7.08)	<0.0001	
LDL cholesterol, mmol/L					
Baseline, mmol/L	3.122 (0.7600)		3.248 (0.8677)		3.286 (0.7792)
Change from baseline, mmol/L	-0.38 (0.060)		-0.41 (0.060)		-0.05 (0.058)
versus placebo	-0.33 (-0.50, -0.17)	<0.0001	-0.36 (-0.53, -0.20)	<0.0001	
Percent change from baseline, %	-10.01 (1.941)		-9.12 (1.918)		0.80 (1.870)
versus placebo	-10.81 (-16.03, -5.58)	<0.0001	-9.92 (-15.15, -4.69)	0.0002	

	Mazdutide 4 mg (N=106)		Mazdutide 6 mg (N=106)		Placebo (N=107)
	Mean	P	Mean	P	Mean
HDL cholesterol, mmol/L					
Baseline, mmol/L	1.151 (0.2392)		1.156 (0.2283)		1.151 (0.2574)
Change from baseline, mmol/L	-0.12 (0.014)		-0.10 (0.014)		-0.05 (0.014)
versus placebo	-0.07 (-0.11, -0.04)	0.0002	-0.05 (-0.09, -0.01)	0.0106	
Change from baseline, %	-9.85 (1.240)		-7.39 (1.250)		-3.49 (1.208)
versus placebo	-6.36(-9.73, -2.99)	0.0002	-3.90 (-7.30, -0.50)	0.0245	
Triglycerides, mmol/L					
Baseline, mmol/L	2.49 (2.047)		2.07 (1.651)		1.92 (1.187)
Change from baseline, mmol/L	-0.31 (0.105)		-0.75 (0.098)		-0.01 (0.097)
versus placebo	-0.30 (-0.58, -0.02)	0.0332	-0.74 (-1.01, -0.47)	<0.0001	
Percent change from baseline, %	-6.60 (5.531)		-19.00 (4.668)		14.71 (4.525)
versus placebo	-21.31(-35.16, -7.46)	0.0026	-33.71 (-46.38, -21.03)	<0.0001	
Serum uric acid, µmol/L					
Baseline, µmol/L	314.56 (94.177)		325.40 (76.402)		318.48 (79.470)
Change from baseline, µmol/L	16.64 (6.680)		-0.04 (6.582)		32.99 (6.357)
versus placebo	-16.35 (-34.28, 1.59)	0.0740	-33.03 (-50.93, -15.13)	0.0003	
ALT, U/L					
Baseline, U/L	26.9 (18.13)		28.7 (18.98)		28.6 (19.53)
Change from baseline, U/L	-6.56 (1.579)		-7.31 (1.573)		2.57 (1.556)
versus placebo	-9.13 (-13.44, -4.83)	<0.0001	-9.88 (-14.20, -5.56)	<0.0001	
AST, U/L					
Baseline, U/L	23.3 (11.24)		25.1 (12.69)		23.8 (12.91)
Change from baseline, U/L	-4.06 (1.050)		-5.29 (1.051)		2.22 (1.051)
versus placebo	-6.28 (-9.18, -3.39)	<0.0001	-7.50 (-10.41, -4.59)	<0.0001	
HOMA2-B, %					
Baseline, %	50.68 (24.503)		46.22 (21.567)		48.62 (21.813)
Change from baseline, %	34.05 (2.725)		40.09 (2.656)		1.35 (2.550)
versus placebo	32.70 (25.43, 39.96)	<0.0001	38.73 (31.54, 45.92)	<0.0001	
HOMA2-IR, %					
Baseline, %	2.280 (1.2028)		2.250 (0.9794)		2.337 (1.0106)
Change from baseline, %	-0.18 (0.073)		-0.41 (0.074)		-0.09 (0.072)
versus placebo	-0.09 (-0.29, 0.11)	0.3690	-0.32 (-0.52, -0.12)	0.0015	
Urine albumin-creatinine ratio*					

	Mazdutide 4 mg (N=106)		Mazdutide 6 mg (N=106)		Placebo (N=107)
	Mean	P	Mean	P	Mean
Baseline	24.775 (1.9452)		23.028 (2.0863)		20.714 (1.5671)
Ratio to baseline	0.50 (0.43, 0.58)		0.54 (0.47, 0.63)		0.76 (0.66, 0.88)
versus placebo	0.65 (0.53, 0.80)	<0.0001	0.71 (0.58, 0.87)	0.0012	

Baseline data are mean (SD) and percent change or change from baseline are LS means (SE), mITT population. Estimated treatment differences are LS means (95% CI). For UACR, baseline data are geometric mean (coefficient of variation) and change from baseline and comparison with placebo are ratio with 95%CI. ANCOVA was used with the treatment group and the stratification factor as fixed effects in the model, and the baseline value of the corresponding outcome variable as covariate. Multiple imputation is used for the missing values. For UACR, data are log-transformed before ANCOVA analysis. All *p* values were two-sided.

ALT=alanine aminotransferase. AST=aspartate aminotransferase. BMI=body mass index. HDL=high density lipoprotein. LDL=low density lipoprotein. HOMA2-B=homeostatic model assessment 2 of β -cell function. HOMA2-IR=homeostasis model assessment 2 of insulin resistance. LS=least squares. mITT=modified intent-to-treat. ANCOVA=analysis of covariance. SE=standard error. CI=confidence interval. UACR=urine albumin-creatinine ratio*.

Supplementary Table 4. Other efficacy outcomes at week 24 reported under the efficacy estimand

	Mazdutide 4 mg (N=106)		Mazdutide 6 mg (N=106)		Placebo (N=107)
	Mean	P	Mean	P	Mean
1,5-Anhydroglucitol, µg/ml					
Baseline, µg/ml	4.8 (4.6)		3.9 (3.4)		4.0 (3.5)
Change from baseline, µg/ml	8.9 (0.6)		10.6 (0.6)		1.6 (0.6)
versus placebo	7.3 (5.6, 9.0)	<0.0001	9.0 (7.2, 10.7)	<0.0001	
Waist circumference, cm					
Baseline, cm	97.72 (11.483)		96.25 (10.688)		98.19 (10.444)
Change from baseline, cm	-3.75 (0.398)		-4.74 (0.404)		-0.48 (0.399)
versus placebo	-3.27 (-4.38, -2.16)	<0.0001	-4.26 (-5.37, -3.14)	<0.0001	
BMI, kg/m²					
Baseline, kg/m ²	28.25 (3.973)		27.80 (3.794)		28.60 (3.983)
Change from baseline, kg/m ²	-1.57 (0.131)		-2.17 (0.132)		-0.36 (0.130)
versus placebo	-1.21 (-1.57, -0.84)	<0.0001	-1.82 (-2.18, -1.45)	<0.0001	
Systolic blood pressure, mm Hg					
Baseline, mm Hg	125.307 (11.6529)		124.748 (12.3997)		127.072 (11.9593)
Change from baseline, mm Hg	-7.48 (1.040)		-6.77 (1.052)		-2.13 (1.056)
versus placebo	-5.35 (-8.26, -2.43)	0.0004	-4.64 (-7.58, -1.70)	0.0021	
Diastolic blood pressure, mm Hg					
Baseline, mm Hg	82.119 (7.8124)		82.075 (7.6790)		82.903 (6.5736)
Change from baseline, mm Hg	-2.53 (0.729)		-2.33 (0.740)		0.35 (0.746)
versus placebo	-2.87 (-4.93, -0.82)	0.0063	-2.67 (-4.74, -0.60)	0.0115	
Total cholesterol, mmol/L					
Baseline, mmol/L	4.88 (1.004)		4.94 (1.125)		4.97 (1.049)
Change from baseline, mmol/L	-0.61 (0.082)		-0.71 (0.084)		-0.11 (0.084)
versus placebo	-0.51 (-0.74, -0.27)	<0.0001	-0.60 (-0.84, -0.37)	<0.0001	
Percent change from baseline, %	-10.96 (1.615)		-12.04 (1.647)		-0.97 (1.661)
versus placebo	-9.99 (-14.55, -5.43)	<0.0001	-11.07 (-15.68, -6.47)	<0.0001	
LDL cholesterol, mmol/L					
Baseline, mmol/L	3.122 (0.7600)		3.248 (0.8677)		3.286 (0.7792)
Change from baseline, mmol/L	-0.38 (0.065)		-0.42 (0.066)		-0.05 (0.066)
versus placebo	-0.33 (-0.51, -0.15)	0.0004	-0.38 (-0.56, -0.19)	<0.0001	
Percent change from baseline, %	-9.86 (2.038)		-9.27 (2.068)		0.29 (2.085)
versus placebo	-10.15 (-15.89, -4.40)	0.0006	-9.56 (-15.34, -3.78)	0.0013	
HDL cholesterol, mmol/L					
Baseline, mmol/L	1.151 (0.2392)		1.156 (0.2283)		1.151 (0.2574)

	Mazdutide 4 mg (N=106)		Mazdutide 6 mg (N=106)		Placebo (N=107)
	Mean	P	Mean	P	Mean
Change from baseline, mmol/L	-0.12 (0.015)		-0.11 (0.015)		-0.04 (0.015)
versus placebo	-0.08 (-0.12, -0.04)	0.0002	-0.06 (-0.10, -0.02)	0.0055	
Percent change from baseline, %	-9.92 (1.310)		-7.62 (1.334)		-3.18 (1.353)
versus placebo	-6.74 (-10.45, -3.03)	0.0004	-4.44 (-8.18, -0.70)	0.0200	
Triglycerides, mmol/L					
Baseline, mmol/L	2.49 (2.047)		2.07 (1.651)		1.92 (1.187)
Change from baseline, mmol/L	-0.34 (0.103)		-0.80 (0.105)		-0.16 (0.107)
versus placebo	-0.19 (-0.48, 0.11)	0.2120	-0.64 (-0.94, -0.35)	<0.0001	
Percent change from baseline, %	-10.55 (4.002)		-22.61 (4.063)		9.59 (4.155)
versus placebo	-20.14 (-31.52, -8.75)	0.0006	-32.20 (-43.64, -20.76)	<0.0001	
Serum uric acid, µmol/L					
Baseline, µmol/L	314.56 (94.177)		325.40 (76.402)		318.48 (79.470)
Change from baseline, µmol/L	18.34 (6.733)		-3.99 (6.863)		26.78 (6.935)
versus placebo	-8.44 (-27.46, 10.59)	0.3834	-30.77 (-49.98, -11.56)	0.0018	
ALT, U/L					
Baseline, U/L	26.9 (18.13)		28.7 (18.98)		28.6 (19.53)
Change from baseline, U/L	-7.45 (1.719)		-8.51 (1.752)		2.61 (1.764)
versus placebo	-10.05 (-14.90, -5.21)	<0.0001	-11.12 (-16.01, -6.23)	<0.0001	
AST, U/L					
Baseline, U/L	23.3 (11.24)		25.1 (12.69)		23.8 (12.91)
Change from baseline, U/L	-4.59 (1.198)		-5.84 (1.222)		2.43 (1.222)
versus placebo	-7.02 (-10.39, -3.65)	<0.0001	-8.27 (-11.68, -4.87)	<0.0001	
HOMA2-B, %					
Baseline, %	50.68 (24.503)		46.22 (21.567)		48.62 (21.813)
Change from baseline, %	35.85 (2.734)		43.11 (2.807)		0.01 (2.807)
versus placebo	35.85 (28.13, 43.56)	<0.0001	43.10 (35.29, 50.91)	<0.0001	
HOMA2-IR, %					
Baseline, %	2.280 (1.2028)		2.250 (0.9794)		2.337 (1.0106)
Change from baseline, %	-0.19 (0.074)		-0.45 (0.076)		-0.08 (0.077)
versus placebo	-0.11 (-0.32, 0.10)	0.2866	-0.37 (-0.59, -0.16)	0.0006	
Urine albumin-creatinine ratio					
Baseline	24.775 (1.9452)		23.028 (2.0863)		20.714 (1.5671)
Ratio to baseline	0.48 (0.41, 0.56)		0.52 (0.45, 0.61)		0.79 (0.67, 0.93)
versus placebo	0.61 (0.49, 0.76)	<0.0001	0.66 (0.53, 0.83)	0.0004	

Baseline data are mean (SD) and percent change or change from baseline are LS means (SE), mITT population. Estimated treatment differences are LS means (95%

CI). For UACR, baseline data are geometric mean (coefficient of variation) and change from baseline and comparison with placebo are ratio with 95%CI. The MMRM models were used, which included fixed categorical effects of treatment group, visit, treatment-by-visit interaction, and the stratification factor, the baseline value of the corresponding outcome variable as covariate, and participant as random effect. Missing data were implicitly handled by using MMRM under the assumption of missing at random for the missing endpoints. For UACR, data were log-transformed before MMRM analysis. All *p* values were two-sided. ALT=alanine aminotransferase. AST=aspartate aminotransferase. BMI=body mass index. HDL=high density lipoprotein. LDL=low density lipoprotein. HOMA2-B=homeostatic model assessment 2 of β -cell function. HOMA2-IR=homeostasis model assessment 2 of insulin resistance. LS=least squares. mITT= modified intent-to-treat. MMRM=mixed model repeated measures. SE=standard error. CI=confidence interval. UACR=urine albumin-creatinine ratio

Supplementary Table 5. Efficacy outcomes at week 48

	Mazdutide 4 mg		Mazdutide 6 mg		Placebo	
	N	Mean	N	Mean	N	Mean
HbA_{1c}, %						
Baseline, %	106	8.19 (0.760)	106	8.21 (0.834)	107	8.33 (0.780)
Week 48, %	89	6.49 (0.792)	90	6.27 (0.904)	101	6.32 (0.683)
Change from baseline, %	89	-1.67 (1.001)	90	-1.95 (1.134)	101	-2.01 (1.003)
< 7%, n (%)	89	60 (67.4)	90	72 (80.0)	101	84 (83.2)
≤6.5%, n (%)	89	49 (55.1)	90	63 (70.0)	101	74 (73.3)
< 5.7%, n (%)	89	17 (19.1)	90	21 (23.3)	101	12 (11.9)
Body weight, kg						
Baseline, kg	106	78.06 (15.886)	106	76.11 (15.049)	107	78.99 (13.377)
Week 48, kg	89	73.10 (16.854)	91	70.02 (15.251)	101	71.92 (13.118)
Change from baseline, kg	89	-6.38 (4.428)	91	-7.34 (5.246)	101	-6.86 (4.009)
Percent change from baseline, %	89	-8.30 (5.660)	91	-9.60 (6.635)	101	-8.76 (4.903)
Weight loss ≥5%, n (%)	89	62 (69.7)	91	65 (71.4)	101	79 (78.2)
Weight loss ≥10%, n (%)	89	28 (31.5)	91	43 (47.3)	101	38 (37.6)
Weight loss ≥5% and HbA _{1c} <7.0%, n (%)	89	45 (50.6)	90	60 (66.7)	101	69 (68.3)
Fasting plasma glucose, mmol/L						
Baseline, mmol/L	106	9.334 (1.6977)	106	10.026 (2.7508)	107	9.740 (2.0441)
Week 48, mmol/L	89	6.774 (1.3645)	91	6.653 (1.6121)	100	6.580 (1.2541)
Change from baseline, mmol/L	89	-2.508 (2.1084)	91	-3.380 (3.0375)	100	-3.185 (2.1327)
Daily mean SMBG, mmol/L						
Baseline, mmol/L	105	11.636 (2.2587)	105	11.949 (2.4084)	104	12.140 (2.4634)
Week 48, mmol/L	85	7.789 (1.5857)	83	7.754 (1.6968)	95	7.782 (1.5330)
Change from baseline, mmol/L	85	-3.618 (2.4600)	82	-4.250 (2.9249)	93	-4.541 (2.7558)
1,5-Anhydroglucitol, µg/ml						
Baseline, µg/ml	106	4.8 (4.63)	106	3.9 (3.40)	107	4.0 (3.48)
Week 48, µg/ml	89	13.9 (8.33)	91	13.1 (7.78)	100	12.6 (7.25)
Change from baseline, µg/ml	89	8.9 (7.56)	91	9.2 (7.10)	100	8.6 (7.34)
Waist circumference, cm						
Baseline, cm	106	97.72 (11.483)	106	96.25 (10.688)	107	98.19 (10.444)
Week 48, cm	89	92.72 (12.627)	91	90.18 (11.100)	101	92.25 (10.775)
Change from baseline, cm	89	-5.82 (5.202)	91	-6.97 (5.710)	101	-5.78 (4.591)
BMI, kg/m²						
Baseline, kg/m ²	106	28.25 (3.973)	106	27.80 (3.794)	107	28.60 (3.983)

	Mazdutide 4 mg		Mazdutide 6 mg		Placebo	
	N	Mean	N	Mean	N	Mean
Week 48, kg/m ²	89	26.19 (4.288)	91	25.37 (3.896)	101	26.07 (3.861)
Change from baseline, kg/m ²	89	-2.34 (1.649)	91	-2.72 (2.040)	101	-2.51 (1.472)
Systolic blood pressure, mmHg						
Baseline, mmHg	106	125.307 (11.6529)	106	124.748 (12.3997)	107	127.072 (11.9593)
Week 48, mmHg	89	121.026 (11.1256)	91	120.577 (13.7006)	101	121.149 (13.0945)
Change from baseline, mmHg	89	-5.052 (11.7527)	91	-3.731 (11.4200)	101	-6.122 (12.2051)
Diastolic blood pressure, mmHg						
Baseline, mmHg	106	82.119 (7.8124)	106	82.075 (7.6790)	107	82.903 (6.5736)
Week 48, mmHg	89	79.942 (6.5213)	91	80.359 (9.1435)	101	81.261 (8.9172)
Change from baseline, mmHg	89	-2.532 (6.8586)	91	-1.861 (7.3410)	101	-1.601 (7.8723)
Total cholesterol, mmol/L						
Baseline, mmol/L	106	4.88 (1.004)	106	4.94 (1.125)	107	4.97 (1.049)
Week 48, mmol/L	89	4.49 (1.132)	91	4.51 (0.935)	99	4.38 (1.055)
Change from baseline, mmol/L	89	-0.37 (0.831)	91	-0.41 (0.845)	99	-0.56 (0.939)
LDL cholesterol, mmol/L						
Baseline, mmol/L	106	3.122 (0.7600)	106	3.248 (0.8677)	107	3.286 (0.7792)
Week 48, mmol/L	89	3.028 (0.8476)	91	3.074 (0.7481)	99	2.987 (0.7981)
Change from baseline, mmol/L	89	-0.090 (0.6157)	91	-0.168 (0.7058)	99	-0.270 (0.7223)
HDL cholesterol, mmol/L						
Baseline, mmol/L	106	1.151 (0.2392)	106	1.156 (0.2283)	107	1.151 (0.2574)
Week 48, mmol/L	89	1.159 (0.2471)	91	1.198 (0.2411)	99	1.133 (0.2621)
Change from baseline, mmol/L	89	0.010 (0.1611)	91	0.056 (0.1829)	99	-0.020 (0.2054)
Triglycerides, mmol/L						
Baseline, mmol/L	106	2.49 (2.047)	106	2.07 (1.651)	107	1.92 (1.187)
Week 48, mmol/L	89	1.66 (1.596)	91	1.41 (0.786)	99	1.43 (0.862)
Change from baseline, mmol/L	89	-0.73 (1.677)	91	-0.64 (1.045)	99	-0.51 (1.169)
Serum uric acid, μmol/L						
Baseline, μmol/L	106	314.56 (94.177)	106	325.40 (76.402)	107	318.48 (79.470)
Week 48, μmol/L	89	317.67 (80.967)	91	317.42 (80.761)	99	308.45 (81.481)
Change from baseline, μmol/L	89	-2.65 (69.208)	91	-11.87 (60.355)	99	-9.93 (58.843)
ALT, U/L						
Baseline, U/L	106	26.9 (18.13)	106	28.7 (18.98)	107	28.6 (19.53)
Week 48, U/L	89	18.9 (11.66)	91	20.9 (13.74)	99	20.7 (14.30)
Change from baseline, U/L	89	-8.7 (20.80)	91	-8.4 (18.71)	99	-7.9 (22.03)
AST, U/L						

	Mazdutide 4 mg		Mazdutide 6 mg		Placebo	
	N	Mean	N	Mean	N	Mean
Baseline, U/L	106	23.3 (11.24)	106	25.1 (12.69)	107	23.8 (12.91)
Week 48, U/L	89	18.8 (5.94)	91	19.9 (7.95)	99	18.7 (5.76)
Change from baseline, U/L	89	-5.0 (12.88)	91	-5.6 (11.59)	99	-5.1 (13.60)
HOMA2-B, %						
Baseline, %	106	50.68 (24.503)	105	46.22 (21.567)	107	48.62 (21.813)
Week 48, %	89	94.96 (46.322)	91	92.28 (41.855)	100	96.27 (36.881)
Change from baseline, %	89	43.26 (35.348)	90	44.49 (36.404)	100	48.75 (33.670)
HOMA2-IR, %						
Baseline, %	106	2.280 (1.2028)	105	2.250 (0.9794)	107	2.337 (1.0106)
Week 48, %	89	2.213 (1.3369)	91	1.945 (0.9095)	100	2.113 (0.8073)
Change from baseline, %	89	-0.099 (0.6648)	90	-0.361 (0.7070)	100	-0.169 (0.7678)
Urine albumin-creatinine ratio						
Baseline	105	24.775 (1.9452)	105	23.028 (2.0863)	105	20.714 (1.5671)
Week 48	89	13.448 (1.5788)	90	14.879 (2.1164)	101	13.048 (1.3302)
ratio to baseline	89	0.52 (1.144)	90	0.61 (0.777)	100	0.62 (1.113)

Data are observed mean (SD) for continuous variables, except for urine albumin-creatinine ratio, which are geometric mean (coefficient of variation). Percentage of participants achieving HbA_{1c} and weight reduction goals are calculated by dividing the number of participants achieving goals by the number of participants with corresponding measurement at week 48. All *p* values were two-sided.

ALT=alanine aminotransferase. AST=aspartate aminotransferase. BMI=body mass index. HDL=high density lipoprotein. LDL=low density lipoprotein.

Supplementary Table 6. Summary of the patient reported outcomes

DTSQ scores^a			
Self-perceived hyperglycaemia			
	Mazdutide 4 mg	Mazdutide 6 mg	Placebo
Baseline			
n	106	106	107
Mean (±SD)	2.3(2.18)	2.3(2.07)	2.3(2.11)
Change from baseline at week 24			
n	93	96	103
Mean (±SD)	-1.4(2.51)	-1.2(2.56)	-0.3(2.40)
Change from baseline at week 48			
n	89	91	101
Mean (±SD)	-1.2(2.22)	-1.1(2.57)	-1.4(2.40)
Self-perceived hypoglycaemia			
Baseline			
n	106	106	107
Mean (±SD)	0.8(1.74)	0.8(1.63)	0.5(1.29)
Change from baseline at week 24			
n	93	96	103
Mean (±SD)	-0.3(2.06)	-0.1(2.13)	0.1(1.68)
Change from baseline at week 48			
n	89	91	101
Mean (±SD)	-0.3(1.97)	-0.3(1.69)	-0.0(1.65)
Overall treatment satisfaction			
Baseline			
n	106	106	107
Mean (±SD)	32.0(5.04)	31.5(4.92)	30.7(5.69)
Change from baseline at week 24			
n	93	96	103
Mean (±SD)	1.1(4.39)	1.2(6.02)	1.1(5.25)
Change from baseline at week 48			
n	89	91	101
Mean (±SD)	1.6(5.44)	1.9(5.77)	2.5(5.85)
EQ-5D-5L VAS scores^b			
Overall health states			
	Mazdutide 4 mg	Mazdutide 6 mg	Placebo
Baseline			
n	106	106	107
Mean (±SD)	90.9(8.97)	90.6(8.65)	88.7(11.22)
At week 24			
n	93	96	103

Mean ($\pm$ SD)	91.7(7.87)	90.5(9.02)	89.6(9.03)
At week 48			
n	89	91	101
Mean ($\pm$ SD)	91.5(7.89)	91.9(7.97)	91.1(7.38)

^a. DTSQ=Diabetes treatment satisfaction questionnaire. SD=standard deviation. Treatment satisfaction score ranges from 0 (very dissatisfied) to 6 (very satisfied), comprehensively reflecting participants' satisfaction with treatment. Self-perceived hyperglycaemia score and self-perceived hypoglycaemia score range from 0 (never) to 6 (the majority of the time), with higher scores indicating that participants perceive themselves to be in hyperglycaemic or hypoglycaemic states more frequently.

^b. EQ-5D-5L=EuroQol 5-Dimension 5-Level. SD=standard deviation. Overall health is self-reported by participants using the EQ-5D-5L Visual Analogue Scale, which ranges from 0 (the worst imaginable health states) to 100 (the best imaginable health states).

Statistical Analysis Plan

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

Protocol No.: CIBI362A301

Version No.: **1.0**

Version Date: **Apr. 10, 2024**

Statistician: 

VERSION HISTORY

SAP Version No.	Approval date	Description of Change
1.0	10 Apr. 2024	Finalization

ABBREVIATION

Abbreviation	English full name
ADA	Anti-drug antibody
AEs	Adverse event
AESI	Adverse event of special interest
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under curve
BMI	Body-mass index
CI	Confidence interval
CL	Clearance
C _{max}	Maximum concentration
Cr	Creatinine
DBIL	Direct bilirubin
ECG	Electrocardiograms
eCRF	Electronic case report form
EOT	End of treatment
FPG	Fasting plasma glucose
FSG	Fast serum glucose
FT3	Free triiodothyronine
FT4	Free thyroxine
GGT	Glutamyl transpeptidase
HbA _{1c}	Glycated hemoglobin A _{1c}
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e Antibody
HBeAg	Hepatitis B e Antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HOMA2-B	Homeostatic model assessment 2-Beta
HOMA2-IR	Homeostatic model assessment 2, insulin resistance
HR	Heart rate
INR	International normalized ratio
ITT	Intent-to-treat
IWRS	INTERACTIVE WEB RANDOMIZATION SYSTEM
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
NAb	Neutralizing antibody
NR	Non-responder

NRI	Non-responder imputation
OR	Odds ratio
PD	Pharmacodynamics
PK	Pharmacokinetics
PLT	Platelet
PPS	Per Protocol Set
PT	Preferred Term
RBC	Red blood cell
SAEs	Severe adverse event
SAP	STATISTICAL ANALYSIS PLAN
SMQs	Standardised MedDRA Queries
SOC	System organ class
SS	Safety set
T _{1/2}	Half-life
TBIL	Total bilirubin
TC	Total cholesterol
TEAE(s)	Treatment-emergent adverse event
TG	Triglyceride
T _{max}	Time to peak drug concentration
TP	Total protein
TSH	Thyroid stimulating hormone
UA	Uric Acid
UGLU	Urine glucose
UPRO	Urine protein
URBC	Urine red blood cell
UREA	Urea
UWBC	Urinary white blood cell
V	Volume distribution
WBC	White blood cell
WHO-DD	WHO drug dictionary

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1 INTRODUCTION

This document is the statistical analysis plan (SAP) for the protocol CIBI362A301, formulated according to the protocol " A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Study to Evaluate the Efficacy and Safety of IBI362 in Chinese Patients with Type 2 Diabetes Mellitus Inadequately Controlled by Diet and Exercise Alone (DREAMS-1) " (protocol number CIBI362A301, version 4.0, date Mar. 14, 2024). This SAP summarizes the design and objectives of the protocol and is intended to provide detailed definitions of the endpoints in the protocol and a detailed description of the planned statistical analyses. The final SAP will be approved and signed before the database is locked.

2 PROTOCOL DETAILS

2.1 Study Objectives and Endpoints

Study Objectives	Study Endpoints
Primary Objective	Primary Endpoint
To validate that the change in HbA_{1c} level from baseline 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 loss in the IBI362 group at Week 24 is superior to that in the placebo group.	Week 24: - Proportion of participants with HbA_{1c} < 7.0%; - Proportion of participants with HbA_{1c} < 7.0% and weight loss ≥ 5% from baseline. - Proportion of participants with ≥ 5% weight loss from baseline; - Percent change from baseline in body weight.
Other Secondary Objectives	Other Secondary Endpoints
- To evaluate the effects of IBI362 on cardiovascular and metabolic parameters; - To assess patient-reported outcomes (PROs); - To evaluate the safety and tolerability of IBI362;	<u>Efficacy Endpoints</u> Week 48: - Change in HbA_{1c} from baseline; - Proportion of participants with HbA_{1c} < 7.0%; - Proportion of participants with ≥ 5% weight loss from baseline;

To evaluate the pharmacokinetic (PK) characteristics of IBI362.	- Proportion of participants with $\text{HbA}_{1c} < 7.0\%$ and weight loss $\geq 5\%$; - Percent change from baseline in body weight. Weeks 24 and 48: - Proportion of participants with $\text{HbA}_{1c} \leq 6.5\%$ and $\text{HbA}_{1c} < 5.7\%$; - Changes in fasting plasma glucose (FPG) from baseline; - Change from baseline in serum 1,5-anhydroglucitol (1,5-AG); - Change from baseline in 7-point self-monitored blood glucose (SMBG); - Change from baseline in waist circumference and BMI; - Absolute change from baseline in body weight; - Proportion of participants with $\geq 10\%$ weight loss from baseline; - Change from baseline in systolic and diastolic blood pressure; - Changes in blood lipid levels [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG)] 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 from baseline in patient-reported outcome (PRO) questionnaire scores: Diabetes Treatment Satisfaction Questionnaire (DTSQ) score; european Quality of Life-5 Dimensions (EQ-5D-5L); - Changes in HOMA2-B and HOMA2-IR from baseline.
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	<u>Safety endpoints :</u> • The incidence and severity of adverse events (AEs) and their relationship with the study drug. • Change from baseline in Vital signs, Physical examination, Laboratory test, and Electrocardiogram (ECGs), and incidence of abnormal measurements. • 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). • The changes in PD parameters (fasting insulin and fasting C-peptide) at different time points before and after administration were assessed.
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2.2 Study design

This is a multi-center, randomized, double-blind, placebo-controlled phase III clinical trial to evaluate the efficacy and safety of IBI362 in T2D patients inadequately controlled by diet and exercise alone. This study plans to enroll approximately 300 T2D participants who still do not reach the target HbA_{1c} after at least 2 months of diet and exercise alone. Participants were required to maintain control of diet and exercise throughout the study.

The entire study period includes a 4-week screening period, a 6-week run-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:

Perform relevant investigation, check the inclusion and exclusion criteria, and determine the eligibility of participants.

Run-in period:

Participants who pass the screening will enter the run-in period, during which they will be considered ineligible if they use hypoglycemic drugs prohibited by the study, and they will be withdrawn from the trial before randomization.

During the run-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 run-in period to retest HbA_{1c}, FPG, or fasting serum glucose (FSG) and Weight, and undergo assessment for 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 HbA_{1c} < 8.5% or HbA_{1c} ≥ 8.5% prior to randomization (V3). During the double-blind treatment period, the investigational drug IBI362 and placebo will be blinded to the 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 continuous 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, and the dosage was increased to 4.0 mg after 4 weeks of continuous administration. After 4 weeks of continuous administration, the dosage was increased to 6.0 mg, and the administration lasted for 16 weeks.
- **Placebo group:** QW subcutaneous injection for 24 consecutive weeks.

Study extension period:

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

- **IBI362 4.0 mg group:** Subcutaneous injection QW; IBI362 4.0 mg, continuous administration for 24 weeks.
- **IBI362 6.0 mg group:** Subcutaneous injection QW; IBI362 6.0 mg, continuous administration for 24 weeks.
- **Placebo group:** Switch to IBI362 treatment with the starting dose of IBI362 2.0 mg. After 4 weeks of continuous administration, adjust the dose to IBI362 4.0 mg. After 4 weeks of continuous administration, continue to adjust the dose to IBI362 6.0 mg and the administration lasted for 16 weeks.

Safety follow-up period:

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

The study procedures are shown in the figure below :

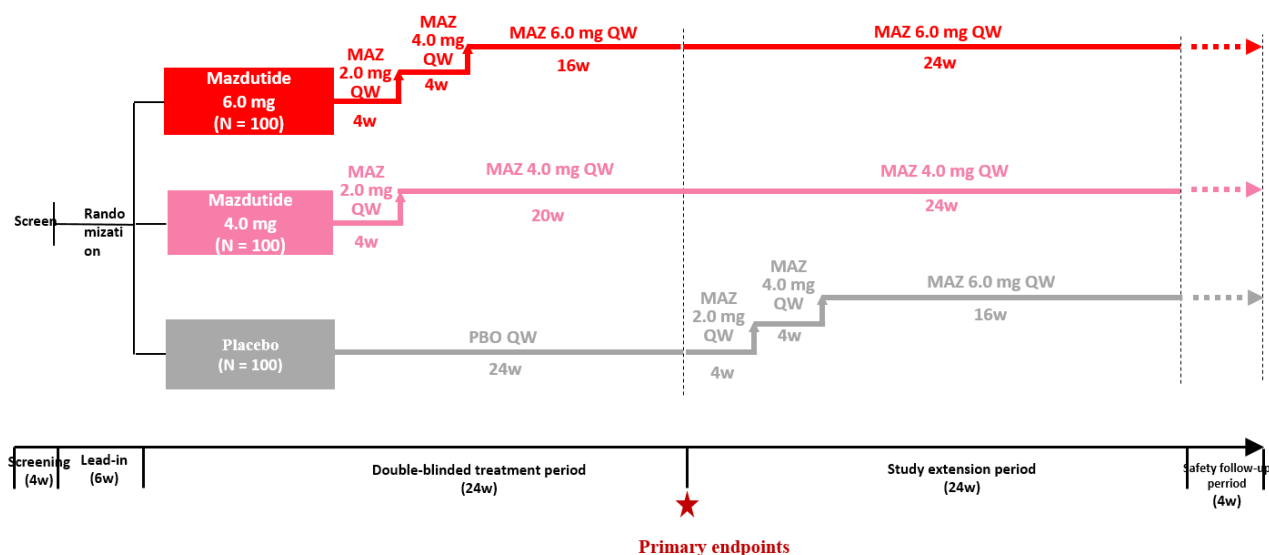


Figure 1. Study Design

2.3 Sample Size and Power

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 are 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 (HbA_{1c} < 8.5% or HbA_{1c} ≥ 8.5%) before randomization (V3). There is a power of more than 99% to observe the statistical superiority of any IBI362 dose group to the placebo group.

2.4 Randomization and Blinding

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. The 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 randomization system manager 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.

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.

2.5 Changes to the planned statistical analysis in the protocol

Protocol	Statistical Analysis Plan	
Statistical description in the protocol	Statistical description in the statistical analysis plan	Reason for change
8.5.2.1 Analysis of primary endpoint Analysis of the Primary Endpoint for Treatment-policy Estimand Analysis of covariance (ANCOVA) will be used, with treatment group <u>and randomization stratification factor</u> as fixed effects and baseline HbA_{1c} as a covariate in the model. Analysis of Primary Endpoint for Efficacy Estimand MMRM will be used, with treatment group, visit, treatment group-by-visit interaction, <u>and randomization stratification factors</u> as the fixed categorical effects, and baseline HbA_{1c} as the covariate.	7.3.1 Analysis of primary endpoint Analyses Under the Treatment-policy Estimand Main analysis An analysis of covariance (ANCOVA) model will be used, with treatment group as a fixed effect and baseline HbA_{1c} as a covariate. Analyses Under the Efficacy Estimand Main analysis The MMRM was used, with treatment group, visit, treatment group-by-visit interaction as fixed categorical effects, and baseline HbA_{1c} as a covariate in the model.	Considering that the baseline HbA_{1c} has been included in the model for adjustment, the stratification factor HbA_{1c} level (HbA_{1c} < 8.5% vs. HbA_{1c} ≥ 8.5%) at randomization (V3) will not be included in the model for analysis of primary endpoint

3 ENDPOINTS

The assessment schedule for the endpoints of this study is shown in [Appendix 1 Schedule of Activities](#).

3.1 Primary efficacy endpoint

Change from baseline in HbA_{1c} at week 24.

3.2 Key Secondary Efficacy Endpoints

1. Proportion of participants with $\text{HbA}_{1c} < 7.0\%$ at week 24;
2. Proportion of participants with $\text{HbA}_{1c} < 7.0\%$ and $\geq 5\%$ reduction in body weight from baseline at week 24;
3. Proportion of participants with $\geq 5\%$ weight loss from baseline at week 24;
4. Percent change in body weight from baseline at week 24.

3.3 Other Secondary Efficacy Endpoints

- Week 48:
 - Change in HbA_{1c} from baseline;
 - Proportion of participants with $\text{HbA}_{1c} < 7.0\%$;
 - Weight Proportion of participants with a decrease of $\geq 5\%$ from baseline;
 - Proportion of participants with $\text{HbA}_{1c} < 7.0\%$ and Weight reduction of $\geq 5\%$;
 - Weight Percentage change from baseline.
- Weeks 24 and 48:
 - Proportion of participants with $\text{HbA}_{1c} \leq 6.5\%$ and $\text{HbA}_{1c} < 5.7\%$;
 - Change from baseline in fasting plasma glucose (FPG);
 - Change from baseline in serum 1,5- Dehydration glucitol (1,5-AG);
 - Change from baseline in 7-point SMBG;
 - Waist circumference and change from baseline in BMI;
 - Weight Absolute change from baseline;
 - Weight Proportion of participants with a decrease of $\geq 10\%$ from baseline;
 - Change from baseline in systolic blood pressure and diastolic blood pressure;
 - Changes in blood lipids [total cholesterol (TC), Low density lipoprotein cholesterol (LDL-C), High density lipoprotein cholesterol (HDL-C), and triglycerides (TG)] from baseline;
 - Change from baseline in Blood uric acid (UA);

-
- Alanine aminotransferase (ALT) and aspartate Ammonia aminotransferase Metastasis (AST) levels from baseline;
 - Change from baseline in Albumin urine /creatinine ratio;
 - Change from baseline in patient-reported outcome (PRO) questionnaire scores: Diabetes mellitus management Satisfaction Questionnaire (DTSQ) score; european Quality of Life-5 Dimensions (EQ-5D-5L);
 - Changes in HOMA-B and Insulin resistance (HOMA2-IR) from baseline.

3.4 Safety Endpoints

- Adverse event (AE) incidence, severity, and relationship to study drug.
- Change from baseline in Vital signs, Physical examination, Laboratory test, and Electrocardiogram (ECG), and incidence of abnormal measurements.
- To evaluate the immunogenicity of IBI362.

3.5 Pharmacokinetic Endpoints and Pharmacodynamics

- 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 the concentration-time curve (AUC), volume of distribution (V), half-life (T_{1/2}), and clearance (CL).
- The changes in PD parameters (fasting insulin and fasting C-peptide) at different time points before and after administration were assessed.

4 ESTIMANDS

4.1 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 participants inadequately controlled by diet and exercise alone, regardless of whether the participants complete the entire treatment with IBI362 in accordance with the protocol.

- **Population:** T2D participants who meet the inclusion/exclusion criteria, have been successfully run-in and have inadequately controlled diet and exercise with at least one dose of the study drug.
- **Treatment:**
 - IBI362 4.0 mg dose group: The starting dose was 2.0 mg, administered once a week for 4 consecutive weeks, and then increased to 4.0 mg for 44 consecutive weeks.
 - IBI362 6.0 mg dose group: The starting dose was 2.0 mg, administered once a week for 4 consecutive weeks, and then increased to 4.0 mg, administered once a week for 4 consecutive weeks, and then increased to 6.0 mg, administered once a week for 40 consecutive weeks.
 - Placebo group: administered for 24 consecutive weeks in the double-blind treatment period, with the method of administration and dosage form consistent with those in the IBI362 group. During the extension period of the study, participants switched to IBI362 2.0 mg once a week for 4 consecutive weeks, followed by an increase to 4.0 mg, and then to 6.0 mg once a week for 4 weeks, for a total of 16 weeks.
- **Endpoint:** 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 reason.	Treatment policy strategy: Data after intercurrent events will continue to be used.	This strategy reflects real-world use of the investigational drug, and the use of the treatment policy strategy allows for assessment of efficacy across drug use scenarios.

- **Population-level summary :** To summarize the efficacy of each efficacy endpoint in the IBI362 4.0 mg and 6.0 mg groups after 24 and 48 weeks of continuous administration, and the IBI362 4.0 mg and 6.0 mg groups compared with the placebo group after 24 weeks of continuous administration in the double-blind treatment period.

4.2 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 participants inadequately controlled by diet and exercise alone, if the participants complete the entire treatment with IBI362 in accordance with the protocol.
- **Population:** T2D participants who meet the eligibility criteria, are successfully enrolled, randomized, and have inadequately controlled after diet and exercise alone with at least one dose of the study drug.
- **Treatment:**

- IBI362 4.0 mg dose group: The starting dose was 2.0 mg, administered once a week for 4 consecutive weeks, and then increased to 4.0 mg for 44 consecutive weeks.
- IBI362 6.0 mg dose group: The starting dose was 2.0 mg, administered once a week for 4 consecutive weeks, and then increased to 4.0 mg, administered once a week for 4 consecutive weeks, and then increased to 6.0 mg, administered once a week for 40 consecutive weeks.
- Placebo group: administered for 24 consecutive weeks in the double-blind treatment period, with the method of administration and dosage form consistent with those in the IBI362 group. During the extension period of the study, participants switched to IBI362 2.0 mg once a week for 4 consecutive weeks, followed by an increase to 4.0 mg, and then to 6.0 mg once a week for 4 weeks, for a total of 16 weeks.
- **Endpoint:** Primary efficacy endpoint and key secondary efficacy endpoint.
- **Intercurrent events and handling strategies:**

Intercurrent event	Handling strategy	Remarks
Premature discontinuation of treatment and use of rescue therapy for any reason	Hypothetical strategy: The efficacy data after the occurrence of an 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 strategy reflects the efficacy of the investigational drug under ideal conditions. As efficacy endpoints may be confounded with non-study medications due to both rescue therapies and other therapies after premature treatment discontinuation, a hypothetical strategy can be used to rule out potentially confounding efficacy.

- **Population-level summary:** The efficacy of each efficacy endpoint after 24 weeks of continuous administration during the double-blind treatment period in the IBI362 4.0 mg group and 6.0 mg group vs. the placebo group will be summarized.

5 ANALYSIS DATASETS

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 are randomized and have 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 mITT 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. Safety analyses for the placebo study extension period will be performed only for participants in the placebo group who received study extension medication.

6 DATA HANDLING

6.1 General Rules

All statistical analyses will be performed using SAS 9.4 (or later).

Categorical data will be statistically described by frequency (percentage). Unless otherwise specified, the number of participants in each treatment group in the corresponding study population will be used as the denominator of percentages. Percentages will be rounded to 1 decimal place.

Continuous data will be statistically described using mean $\pm$ standard deviation or median (minimum, maximum). Mean and median will be presented to 1 more decimal place than the raw data, standard deviation will be presented to 2 more decimal places than the raw data, and maximum and minimum will be presented to the same decimal places as the raw data.

Baseline is defined as the last available measurement before the first dose of the investigational drug.

For PK parameters, see the PK Analysis Plan for details.

6.2 Efficacy Data Handling Specifications

Unless otherwise stated in this trial, the efficacy data will not be processed, and the missing values will not be imputed. The methods for imputing missing data of primary and secondary efficacy endpoints are detailed in [Section 7.3](#).

6.3 Missing Values and Outliers

- **Completely/partially missing value in date of prior/concomitant drug/non-drug therapy**

No imputation is required if the start/end date or time of prior/concomitant medication/non-drug therapy is completely or partially missing. Complete or partial missing cases for which prior or concomitant cannot be determined will be considered as concomitant.

- **Completely/partially missing value in study drug administration date**

If the dosing date of an investigational product is completely missing, it will not be imputed. If it is partially missing, the missing date will be reasonably imputed based on the use and time of other non-missing medications of the participant.

- **Completely/partially missing value in date of diabetes diagnosis**

If the diagnosis date of diabetes is completely missing, it will not be imputed. If the day is missing, it will be imputed as the 15th day; if the month is missing, it will be imputed as July.

- **Completely/partially missing value in AE date/time**

If the start date/time of an AE is completely or partially missing, and the data collected by the eCRF cannot determine whether it is before or after the first study dose, the AE will be considered as a TEAE. Unless otherwise stated, completely or partially missing AE dates will not be imputed.

When calculating the dates of TEAEs:

Start Date of Adverse Event:

AE Start Date	Imputation Rule
The year, month, and day are all missing	Impute as the date of the first dose
Month, day missing or only day missing	1. If it is in the same year (or year and month) as the date of the first dose, the date will be imputed as the date of the first dose. 2. Otherwise, use the first day of the known year (or month and year).
Note: After imputation, if the start date is later than the end date, the start date will be imputed with the end date.	

End Date of Adverse Event:

AE End Date	Participant category	Imputation Rule
The year, month, and day are all missing	Participants who prematurely withdrew from the study	Impute with the later of the date of premature study withdrawal or the date of last contact with participant
	Participants not prematurely withdrawing from the study	Impute with data cut-off date
Month, day missing or only day missing	Participants who prematurely withdrew from the study	1. If it is the same year (or year and month) as the date of early withdrawal or the date of last contact with the participant, the date will be imputed as the date of early withdrawal or the date of last contact with the participant, whichever is later. 2. Otherwise, impute as the last day of the known year (or year and month).
	Participants not prematurely	1. If it is in the same year (or year and month) as the data cut-off date, impute the data as the data cut-off date.

	withdrawing from the study	2. Otherwise, impute as the last day of the known year (or year and month).
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- **If the start date/time of the first study dose is missing and the data collected by the eCRF cannot determine whether the AE occurred before or after the first study dose, it will be marked as a TEAE.**

An AE that occurs on or after the day of randomization is considered to be a TEAE.

The above imputation of completely/partially missing date is only used to mark or calculate new variables for summary analysis, and the original date recorded on the eCRF is still listed in the listing.

- **Missing of causality between AE and study drug**

If the relationship between the AE and the study drug was missing, the AE was considered to be related, and no data imputation was required.

- **Missing of severity of adverse events**

In the summary analysis of severe AEs, AEs with missing severity grade will be included in the number of severe cases/frequency. In the analysis of AE grade summary by severity (mild, moderate, and severe), AEs with missing severity grade will be summarized separately as "missing".

- **Missing at baseline**

For efficacy endpoints with missing baseline values and non-laboratory efficacy data such as body weight, the first post-baseline test results will be used for imputation; for central laboratory test data with local laboratory test results, the baseline test results of the corresponding local laboratory will be used for imputation.

Other missing baseline indicators will not be imputed unless otherwise specified.

Participants with missing baseline values will be classified as "missing" in a cross tabulation summarizing baseline and worst post-baseline results.

- **Outlier Handling**

There was no planned examination and handling of outliers in this study.

- **Other Data Handling Considerations**

If the reported value of a laboratory parameter cannot be used in a statistical summary table (e.g., the value of a numeric parameter is reported as a string), the coded value will be determined appropriately and used in the statistical analysis. Typically the upper limit of the assay will be increased by 0.0001, e.g. ">100" will be considered as "100.0001"; typically lower than the lower limit of the assay will be decreased by 0.0001, e.g. "<100" will be considered as "99.9999". The actual values as reported in the database will still be presented in the listings.

6.4 Time Points and Visit Windows

For by-visit summaries, only scheduled visits were used.

Use of data from unscheduled visits:

Unscheduled visit data will be used for baseline value labeling. The unscheduled visit data of safety indicators such as laboratory tests, vital signs, and ECG will be used to analyze the changes from normal to abnormal before and after baseline (crosstab), but will not be used for the analysis summarized by visits.

7 Statistical Analysis Methods

7.1 Participant Disposition and Protocol Deviations

7.1.1 Disposition of Participants

The number and percentage of participants who enter the screening and run-in periods and the reasons for screening or run-in failure will be summarized. The distribution of participants will be summarized by site.

In the intention-to-treat (ITT) set, the number of randomized participants and the number of participants who have received at least one dose of the investigational product are summarized by treatment group. The number, percentage, and reasons of participants who prematurely discontinued the study drug and withdrew from the study during the double-blind treatment period and the study extension period were summarized and listed. A listing of inclusion or exclusion will be provided for each participant.

7.1.2 Protocol Deviation

In the intention-to-treat (ITT) set, the number and percentage of participants with major protocol deviations and those excluded from the PPS during the study will be summarized by group and protocol deviation type, and all participants with protocol deviations will be listed.

A detailed list of the inclusion and exclusion of individual participants from the PPS will be provided.

7.2 Demographic and Other Baseline Characteristics

7.2.1 Demographic and Baseline Characteristics

In the intention-to-treat (ITT) set, the descriptive statistics of demographic data and baseline characteristics will be summarized by group.

Continuous variables will be summarized using the number of participants, mean, standard deviation, median, Q1 and Q3, minimum, and maximum. The number and percentage of participants were summarized for categorical variables.

- Age (years) = (date of signing ICF – date of birth + 1)/365.25, rounded to the nearest integer; and its categorical variables;
- Height (cm);
- Baseline body weight (kg) and its categorical variables;
- Baseline BMI (kg/m^2) and its categorical variables;
- Gender: male, female;
- Ethnicity: Han Chinese, others;
- Smoking status: Never smoke, smoker, quit smoking;
- Alcohol use: Never drink alcohol, drink alcohol, quit drinking;
- Duration of type 2 diabetes = (date of randomization - initial diagnosis + 1)/365.25, rounded to the smallest integer; and its categorical variables;
- Baseline HbA_{1c} (%) and its categorical variables;
- Baseline FPG (mmol/L);
- Baseline eGFR (mL/min/1.73m^2), and its categorical variables.

Baseline values of other indicators such as waist circumference, systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, LDL-C, HDL-C, blood uric acid, ALT, AST, and urine albumin/creatinine ratio will also be summarized.

Randomization stratification factors will be summarized by group according to the data in the CRF and IWRS system.

Demographics and baseline characteristics of participants will be listed.

7.2.2 Comorbidity

In the intention-to-treat (ITT) set, the comorbidities of the participants during the screening period will be summarized by group. See [Appendix 2](#) for the derive rules.

- Hypertension

-
- Dyslipidaemia
 - Hyperuricemia/gout
 - Hepatic function abnormal
 - Fatty liver

7.2.3 Diabetes-related complications

In the intention-to-treat (ITT) set, diabetes-related complications of participants during the screening period will be summarized by group. See [Appendix 3](#) for the derive rules.

- Retinopathy
- Neuropathy
- Nephropathy

7.2.4 Medical history

Medical history will be coded using the MedDRA dictionary (version 26.0 or higher). In the intention-to-treat (ITT) set, the number and percentage of participants with medical history were summarized by group, preferred SOC, and PT. If a participant has multiple medical histories in the same category of SOC or PT, the participant will be counted only once in the category of SOC or PT.

The details of participants' medical history will be listed.

7.2.5 Prior/Concomitant Medications

Prior/concomitant medications will be coded using the WHO-DD (WHO-drug dictionary) (version WHODrug B3GL 202303 or higher). In the intent-to-treat (ITT) set, the number and percentage of participants with prior/concomitant medications were summarized by group, ATC level 2, ATC level 4, and PN for prior/concomitant medications, respectively. If ATC level 2 or ATC level 4 was not available, the latest level with a value was used. If a participant had multiple concomitant medications in the same ATC level 2, ATC level 4, or PN category, the participant was counted only once in the ATC level 2, ATC level 4, or PN category.

A prior medication is defined as a medication that has been started before the first dose of the study drug and stopped before the first dose of the study drug .

Concomitant medications are defined as drugs that have been taken from the start of the first study dose to the last study dose + 56 days, including drugs that have been taken before the first study dose and are still taken after the first study dose, and drugs that have been taken on or after the day of the first study dose to the last study dose + 56 days.

Concomitant medications during the double-blind treatment period are defined as medications that are taken from the start of the first dose of study drug to the first dose of study drug in the extension period (excluding the day of the first dose of study drug in the extension period). Concomitant medications during the extension period of the study were defined as medications taken from the start of first study extension dose until the last study extension dose + 56 days.

Concomitant medications in the two IBI362 dose groups and the placebo group during the double-blind treatment period will be summarized separately. In addition, concomitant medications in the two IBI362 dose groups during the entire treatment period and concomitant medications in the placebo group during the extension period will also be summarized separately.

Prior/concomitant medications were listed.

7.2.6 Prior/Concomitant Non-Drug Therapies

Prior and concomitant non-drug therapies will be coded using the MedDRA dictionary (version 26.0 or higher). In the intent-to-treat (ITT) set, the number and percentage of participants receiving concomitant non-drug therapies will be summarized by treatment group, preferred SOC, and PT. If a participant has multiple prior and concomitant non-drug therapies within the same SOC or PT, the participant will be counted only once for that SOC or PT.

Prior non-drug therapy is defined as a non-drug therapy that has been started before the first dose of the investigational product and stopped before the first dose of the investigational product.

Concomitant non-drug therapies are defined as non-drug therapies that are initiated or continued from the first dose of the study drug to the last dose of the study drug + 56 days, including non-drug therapies that have been initiated before the first dose of the study drug and are continued after the first dose of the study drug, as well as non-drug therapies that are initiated on or after the day of the first dose of the study drug to the last dose of the study drug + 56 days.

Concomitant non-drug therapy during the double-blind treatment period is defined as non-drug therapy that is started or continued after the start of the first dose of the study drug and before the first dose in the extension period (excluding the day of the first dose in the extension period). Concomitant medications in the extension period of the study are defined as non-drug therapies started after the start of the first dose during the extension period of the study until the last dose in the extension period of the study + 56 days or continued.

The concomitant non-drug therapies in the two IBI362 dose groups and the placebo group during the double-blind treatment period will be summarized separately. In addition, the concomitant non-drug therapies in the two IBI362 dose groups during the entire treatment period will be summarized separately, and the concomitant non-drug therapies in the placebo group during the extension period will also be summarized separately.

Prior/concomitant non-drug therapies will be listed.

7.2.7 COVID-19 infection

COVID-19 infection (infected, suspected infected, unknown, and not infected), related symptoms, impact on study medication, and impact on visits will be summarized and listed.

7.2.8 Intercurrent event

The intercurrent events for this study were premature discontinuation of treatment and use of rescue therapy for hyperglycemia. If a participant experiences multiple occurrences of an intercurrent event during the study, the earliest occurrence of the intercurrent event will be used for calculation. If both premature treatment discontinuation and rescue therapy for hyperglycemia occurred, it was calculated as rescue therapy for hyperglycemia.

For the occurrence date of intercurrent events, the intercurrent event date of premature discontinuation of the study drug is the date of the last dose of the study drug + 10 days (including the 3-day visit window); for rescue therapy of hyperglycemia, the earliest use or occurrence date of rescue therapy should be used.

The occurrence and time of intercurrent events will be summarized by group. Intercurrent events will be tabulated.

7.3 Analysis of Efficacy

All primary and secondary efficacy endpoints were analyzed in the modified intention-to-treat (mITT) set.

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

The primary endpoint of this study is the change in HbA_{1c} from baseline at week 24. For marketing registration application, the efficacy analysis will be mainly based on the treatment-policy estimand, and the IBI362 group will be considered superior to the placebo group when the primary endpoint is reached based on the treatment-policy estimand. The efficacy estimand is only used as supporting evidence. Other non-registration purposes, such as publication of articles, will be mainly based on the efficacy estimand, and when the primary endpoint under the efficacy estimand is reached, the IBI362 group will be considered superior to the placebo group. Since the clinical questions answered by the two estimands and the application objectives of the two estimands were different, no multiplicity adjustment was performed between the two estimands.

The type of intercurrent event and the time point of occurrence will be determined by directly deriving the corresponding information on the corresponding page through the eCRF. If the same participant has experienced two intercurrent events in succession, the earlier intercurrent event will be derived. If two intercurrent events occur at the same time, rescue therapy for hyperglycemia will be taken. For the judgment of the onset date of intercurrent events, please refer to Section 7.2.8.

Table 1. Summary of efficacy endpoint analysis

Parameter	Estimands	Analysis	Note: Analyzed or not
Primary endpoint	Treatment-policy estimand	Main analysis	√
		Sensitivity analysis 1	√
		Sensitivity Analysis 2	√
		Sensitivity Analysis 3	√
		Supplementary analysis	√
	Efficacy Estimands	Main analysis	√
		Supplementary analysis	√
(Key) Secondary continuous endpoints#	Treatment-policy estimand	Main analysis	√
		Sensitivity analysis 1	Key Secondary Endpoints Analysis Only
		Sensitivity Analysis 2	Key Secondary Endpoints Analysis Only
		Sensitivity Analysis 3	Key Secondary Endpoints Analysis Only
		Supplementary analysis	√
	Efficacy Estimands	Main analysis	√
		Supplementary analysis	√
(Key) Secondary		Main analysis	√

categorical endpoints	Treatment-policy estimand	Sensitivity analysis 1	Key Secondary Endpoints Analysis Only
		Sensitivity Analysis 2	Key Secondary Endpoints Analysis Only
		Sensitivity Analysis 3	Key Secondary Endpoints Analysis Only
		Supplementary analysis	√
	Efficacy Estimands	Main analysis	√
		Supplementary analysis	√

#: In addition to the secondary endpoints defined in the protocol, this analysis also included the PD endpoints: fasting insulin and fasting C-peptide. Change from baseline in patient-reported outcome questionnaire scores: Diabetes mellitus management The Satisfaction Questionnaire (DTSQ) and the EuroQoL 5-Dimension 5-Level questionnaire (EQ-5D-5L) will be participated to descriptive statistical analysis only.

This table only summarized the efficacy endpoints at Week 24; the efficacy endpoints at Week 48 were only analyzed descriptively.

Table 2. Summary of analysis methods for efficacy endpoints.

Parameter	Estimands	Analysis	Analytical Method	Handling of Missing Data
Primary endpoint	Treatment-policy estimand	Main analysis	ANCOVA	Missing data due to intercurrent events: multiple imputation is performed using the data of participants in the same group who have experienced intercurrent events but have collected the measurement results at the corresponding visit Missing data not due to intercurrent events: multiple imputation is performed using the measurement results at the corresponding visit collected in the same group
		Sensitivity analysis 1		Missing data due to intercurrent events: Multiple imputation is performed using data from participants in the same group who experience intercurrent events but have corresponding visit measurements collected Missing data not due to intercurrent events: Multiple imputation is performed using corresponding visit measurements collected from the placebo group
		Sensitivity Analysis 2		LOCF
		Sensitivity Analysis 3		R2B (Return to Baseline)
		Sensitivity Analysis 4		A tipping point analysis was performed after imputing missing data using the same method as that used in the primary analysis
		Supplementary analysis		The analytical method and missing value imputation method were the same as those for the main analysis, and the analysis set was the PPS

	Efficacy Estimands	Main analysis	MMRM	The MMRM model under missing at random (MAR)
		Supplementary analysis		The analytical method and missing value imputation method were the same as those for the main analysis, and the analysis set was the PPS
24-week continuous Secondary Endpoints	Treatment-policy estimand	Main analysis	ANCOVA	Missing data due to intercurrent events: multiple imputation is performed using the data of participants in the same group who have experienced intercurrent events but have collected the measurement results at the corresponding visit Missing data not due to intercurrent events: multiple imputation is performed using the measurement results at the corresponding visit collected in the same group
		Sensitivity analysis 1		Missing data due to intercurrent events: Multiple imputation is performed using data from participants in the same group who experience intercurrent events but have corresponding visit measurements collected Missing data not due to intercurrent events: Multiple imputation is performed using corresponding visit measurements collected from the placebo group
		Sensitivity Analysis 2		LOCF
		Sensitivity Analysis 3		R2B (Return to Baseline)
		Supplementary analysis		The analytical method and missing value imputation method were the same as those for the main analysis, and the analysis set was the PPS
	Efficacy Estimands	Main analysis	MMRM	The MMRM model under missing at random (MAR)
		Supplementary analysis		The analytical method and missing value imputation method were the same as those for the main analysis, and the analysis set was the PPS
24-Week Categorical Secondary Endpoints	Treatment-policy estimand	Main analysis	Logistic regression	Missing data due to intercurrent events: Derived as categorical variables after multiple imputation using data of participants in the same group who have experienced intercurrent events but have collected measurement results at the corresponding visit Missing data not due to intercurrent events: Derived as categorical variables after multiple imputation using measurement results at the corresponding visit collected in the same group

		Sensitivity analysis 1		Missing data due to intercurrent events: Derived as categorical variables after multiple imputation using data from participants in the same group who have experienced intercurrent events but have collected measurement results at the corresponding visit Missing data not due to intercurrent events: Derived as categorical variables after multiple imputation using corresponding visit measurement results collected from the placebo group
		Sensitivity Analysis 2		LOCF
		Sensitivity Analysis 3		NRI
		Supplementary analysis	Logistic regression	The analytical method and missing value imputation method were the same as those for the main analysis, and the analysis set was the PPS
	Efficacy Estimands	Main analysis	Logistic regression	Derived after imputation using multiple imputation (MI) method under MAR mechanism
		Supplementary analysis		The analytical method and missing value imputation method were the same as those for the main analysis, and the analysis set was the PPS

7.3.1 Analysis of primary endpoint

The primary endpoint in this study was the change from baseline in HbA_{1c} at Week 24.

- Analyses Under the Treatment-policy Estimand**

Main analysis:

An analysis of covariance (ANCOVA) model will be used, with treatment group as a fixed effect and baseline HbA_{1c} as a covariate. Considering that the baseline HbA_{1c} has been included in the model for adjustment, the randomization stratification factors HbA_{1c} level before randomization (V3) (HbA_{1c} < 8.5% vs. HbA_{1c} ≥ 8.5%) will not be included in this model for model fitting. The least squares mean of the change in HbA_{1c} from baseline in the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group and its 95% CI were calculated, and the difference estimates between the two IBI362 dose groups and the placebo group, the corresponding standard error, 95% CI, and the corresponding p value were provided. When the superiority test of the IBI362 group vs. the placebo group is significant (p < 0.05), it can be considered that the statistical superiority of the IBI362 group vs. the placebo group has been demonstrated.

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 after the occurrence of intercurrent events, multiple imputation will be performed using the data of participants in the same treatment group who have experienced intercurrent events but have HbA_{1c} measurement results collected at week 24. If intercurrent events occur but there are too few data from participants in the same treatment group with HbA_{1c} 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 treatment group with HbA_{1c} measurements collected.

Imputation of missing values not due to intercurrent events:

For missing values not caused by intercurrent events, multiple imputation will be performed using data from all participants in the same group whose HbA_{1c} test results are collected.

Sensitivity analysis 1:

The model is the same as the main analysis, using ANCOVA, with treatment group as the fixed effect and baseline HbA_{1c} as the covariate in the model.

Imputation of missing values due to or not due to intercurrent events:

For missing data after the intercurrent event, multiple imputation will be performed using data from participants in the same group who have experienced the intercurrent event but whose HbA_{1c} measurement at Week 24 is collected (if the model does not converge due to too little data from participants in the same group who have experienced the intercurrent event but whose HbA_{1c} measurement at Week 24 is collected, multiple imputation will be performed using data from all participants in the same group whose HbA_{1c} measurement is collected). For missing values not due to intercurrent events, multiple imputation will be performed using J2R (Jump to Reference).

Sensitivity analysis 2:

The model was the same as the main analysis.

Imputation of missing values due to or not due to intercurrent events:

Missing data after the intercurrent event and missing values not caused by the intercurrent event will be imputed using last observation carried forward (LOCF).

Sensitivity analysis 3:

The model was the same as the main analysis.

Imputation of missing values due to or not due to intercurrent events:

For missing values caused or not caused by intercurrent events, R2B (Return to Baseline) will be used for imputation.

Sensitivity analysis 4:

The model was the same as the main analysis.

Imputation of missing values due to or not due to intercurrent events:

Missing data were imputed using the same multiple imputation method used for the primary analysis and then analyzed using tipping point analysis.

Supplementary analysis:

The model was the same as the main analysis. The imputation of missing values caused or not caused by intercurrent events is the same as that in the main analysis. The PPS was used for the analysis population.

- **Analyses Under the Efficacy Estimand**

Main analysis:

The MMRM was used, with treatment group, visit, treatment group-by-visit interaction as fixed categorical effects, and baseline HbA_{1c} as a covariate in the model. Considering that the baseline HbA_{1c} has been included in the model for adjustment, the randomization stratification factors HbA_{1c} level before randomization (V3) (HbA_{1c} < 8.5% vs. HbA_{1c} ≥ 8.5%) will not be included in this model for model fitting. Calculate the adjusted least squares estimates and their 95% CIs of the changes in HbA_{1c} from baseline in the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group, respectively. The difference estimates, corresponding standard errors, 95% CIs, and corresponding p-values between the two IBI362 dose groups and the placebo group will also be provided.

An unstructured correlation matrix will be used in the MMRM model to model the within participant error. If the model does not converge, then the first converged model of the following covariance structures from top to bottom will be used:

Toeplitz

First order autoregressive

Compound symmetry

Variance Components

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 intercurrent events. Data after the occurrence of intercurrent events will be handled using the MMRM model by SAS under missing at random (MAR) mechanism.

Imputation of missing values not due to intercurrent events:

Missing data will be handled using the MMRM model by SAS under missing at random (MAR) mechanism.

Supplementary analysis:

The model was the same as the main analysis, and MMRM was used for analysis. The imputation of missing values caused or not caused by intercurrent events is the same as the main analysis, and the PPS is used in the analysis population.

7.3.2 Analysis of secondary efficacy endpoints

Key Secondary Endpoints:

The key secondary endpoints will be analyzed based on the treatment-policy estimand and efficacy estimand, respectively.

Analysis of continuous variables

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

- **Analysis of Continuous Variables Under the Treatment-policy Estimand**

Main analysis:

An ANCOVA model will be used with treatment group and randomization stratification factors as fixed effects and baseline body weight as a covariate. The analysis will be performed using the actual stratification factors of the participants, which will be the data collected in the CRF. The least squares mean of the percentage change in body weight from baseline in the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group and its 95% CI were calculated, and the between-group difference estimates, corresponding standard errors, 95% CI, 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 after the occurrence of intercurrent events, multiple imputation will be performed using the data of participants in the same treatment group who have experienced intercurrent events but have collected the 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 group with weight measurements collected.

Imputation of missing values not due to intercurrent events:

For missing values not caused by intercurrent events, multiple imputation will be performed using the data of all participants in the same group whose body weight test results are collected.

Sensitivity analysis:

The model was the same as the main analysis.

Imputation of missing values due to or not due to intercurrent events:

Missing values due to or not due to the occurrence of intercurrent events will be handled in a manner similar to sensitivity analyses 1, 2, and 3 for the primary endpoint under the treatment-policy estimand.

Supplementary analysis:

The model was the same as the main analysis. The imputation of missing values caused or not caused by intercurrent events is the same as that in the main analysis. The PPS was used for the analysis population.

- **Analysis of Continuous Variables Under the Efficacy Estimand**

Main analysis:

The MMRM will be used, with treatment group, visit, treatment group-by-visit interaction, and randomization stratification factors as the fixed categorical effects, and baseline body weight as the covariate in the model. The analysis will be performed using the actual stratification factors of the participants, which will be the data collected in the CRF. The adjusted least squares estimates and their 95% CIs of the percent changes in body weight relative to baseline will be calculated for the IBI362 4.0 mg group, IBI362 6.0 mg group, and placebo group, respectively. The difference estimates, corresponding standard errors, 95% CIs, and corresponding p-values between the two IBI362 dose groups and the placebo group will also be provided.

An unstructured correlation matrix will be used in the MMRM model to model the within participant error. If the model does not converge, then the first converged model of the following covariance structures from top to bottom will be used:

Toeplitz

First order autoregressive

Compound symmetry

Variance Components

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 intercurrent events. Data after the occurrence of intercurrent events will be handled using the MMRM model by SAS under missing at random (MAR) mechanism.

Imputation of missing values not due to intercurrent events:

Missing data will be handled using the MMRM model by SAS under missing at random (MAR) mechanism.

Supplementary analysis:

The model was the same as the main analysis, and MMRM was used for analysis. The imputation of missing values caused or not caused by intercurrent events is the same as the main analysis, and the PPS is used in the analysis population.

Analysis of categorical variables

- **Analysis of categorical variables under the treatment-policy estimand**

Primary analysis:

Logistic regression will be used, with treatment group and randomization stratification factors as fixed effects in the model, and the baseline value of corresponding parameter as a covariate (for the proportion of participants with $\text{HbA}_{1c} < 7.0\%$ and a $\geq 5\%$ decrease in body weight from baseline, the baseline values of both parameters will be used as covariates). Considering that the analysis of parameters involving HbA_{1c} target rate (the proportion of participants with $\text{HbA}_{1c} < 7.0\%$ and the proportion of participants with $\text{HbA}_{1c} < 7.0\%$ and $\geq 5\%$ weight loss from baseline) has been included the baseline HbA_{1c} as a covariate, the randomization stratification factor HbA_{1c} level before randomization (V3) ($\text{HbA}_{1c} < 8.5\%$ vs. $\text{HbA}_{1c} \geq 8.5\%$) will not be included in this model for model fitting (the analysis model for the proportion of participants with a decrease of $\geq 5\%$ from baseline in Weight will still include the randomization stratification factors as fixed effects). 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 values, were provided. If the model does not converge due to the small number of participants in a group who meet the target, the fifth method will be used for analysis.

Logistic regression will be used to calculate the between-group difference in the rate between the two IBI362 dose groups and the placebo group and its 95% CI. The rate was calculated for each group and the corresponding 95% CI was provided.

Intercurrent events and handling of intercurrent events:

The intercurrent events were premature discontinuation of treatment and use of rescue therapy. Intercurrent events will be handled using the treatment policy strategy, i.e., data collected after the intercurrent event will continue to be used. In the data collected after the occurrence of intercurrent events, if there is missing data in the IBI362 group or the placebo group, multiple imputation will be performed using the data of participants in the same group who have experienced intercurrent events but have collected the efficacy endpoint measurement results at Week 24, and then the efficacy endpoint will be derived based on the imputed data to determine whether the target has been reached.

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 for whom efficacy measurements are collected. Categorical

endpoint will then be derived based on imputed data.

Sensitivity analysis 1:

The model was the same as the main analysis.

Imputation of missing values due to or not due to intercurrent events:

For missing data after an intercurrent event, multiple imputation was performed using data from participants in the same group who experienced the intercurrent event but had the Week 24 efficacy measurements collected.

For missing values not due to intercurrent events, multiple imputation will be performed using J2R. That is, if there is missing value at week 24 not due to intercurrent events in the IBI362 group or the placebo group, the missing data will be multiply imputed using the efficacy endpoint measurements collected from the placebo group at week 24. The categorical efficacy measures will then be derived based on the imputed data.

Sensitivity analysis 2:

The model was the same as the main analysis.

Imputation of missing values due to or not due to intercurrent events:

Missing data after intercurrent events and missing values not due to intercurrent events will be imputed using LOCF.

Sensitivity analysis 3:

The model was the same as the main analysis.

Imputation of missing values due to or not due to intercurrent events:

Missing data after the occurrence of the intercurrent event and missing values not caused by the intercurrent event will be imputed as non-response (non-responder, NR).

Supplementary analysis:

The model was the same as the main analysis.

Imputation of missing values due to or not due to intercurrent events:

The imputation of missing values caused or not caused by intercurrent events is the same as the primary analysis, and the PPS is used in the analysis population.

- **Analysis of categorical variables under the efficacy estimand**

Main analysis:

Logistic regression will be used, with treatment group and randomization stratification factors as fixed effects in the model, and baseline efficacy endpoint as the covariate (for the proportion of participants with $HbA_{1c} < 7.0\%$ and $\geq 5\%$ decrease in body weight from baseline, the baseline values of both parameters will be used as covariates). Considering that the analysis of parameters involving

HbA_{1c} target rate (the proportion of participants with HbA_{1c} < 7.0% and the proportion of participants with HbA_{1c} < 7.0% and ≥ 5% weight loss from baseline) has been included the baseline HbA_{1c} as a covariate, the randomization stratification factor HbA_{1c} level before randomization (V3) (HbA_{1c} < 8.5% vs. HbA_{1c} ≥ 8.5%) will not be included in this model for model fitting (the analysis model for the proportion of participants with a decrease of ≥ 5% from baseline in Weight will still include the randomization stratification factors as fixed effects). The OR and 95% CI of IBI362 4.0 mg group and IBI362 6.0 mg group vs. placebo group, as well as the corresponding p values, were provided. The difference in the rate between the two IBI362 dose groups and the placebo group and its 95% CI will be calculated. The rate of each group was calculated and the corresponding 95% CI was provided.

Intercurrent events and handling of intercurrent events:

The intercurrent events were premature discontinuation of treatment and use of rescue therapy. 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 the intercurrent event. For data after the occurrence of intercurrent events, assuming that the data is missing at random (MAR), the multiple imputation (MI) method under the MAR mechanism will be used to impute the efficacy indicators at week 24, and then derive whether it meets the target.

Imputation of missing values not due to intercurrent events:

Assuming that the data is missing at random (MAR), multiple imputation (MI) under the MAR mechanism will be used to impute the efficacy indicators at week 24, and then derive whether it meets the target.

Supplementary analysis:

The model was the same as the main analysis.

Imputation of missing values due to or not due to intercurrent events:

The imputation of missing values caused or not caused by intercurrent events is the same as the main analysis, and the PPS is used in the analysis population.

Other secondary endpoints:

For other continuous secondary endpoints, the mean, standard deviation, median, maximum, and minimum were provided; for categorical endpoints, the number and percentage of participants were provided.

The following secondary endpoint measures will be model-fitted and analyzed under the analysis framework of the treatment-policy and efficacy estimands: the proportion of participants with HbA_{1c} ≤ 6.5%, FPG, mean 7-point SMBG change from baseline at week 24, proportion of participants with ≥ 10% weight reduction from baseline, Weight absolute change from baseline, Waist circumference, Body mass index, systolic blood pressure, diastolic blood pressure, TC, LDL-C, HDL-C, TG, Blood uric acid, ALT, AST, HOMA2-B, Insulin resistance (HOMA2-IR), and Albumin urine / creatinine

ratio change from baseline. Only descriptive statistical analysis will be performed for each endpoint at Week 48.

For the analysis of 7-point SMBG, the mean of 7 points, mean before meal, mean 2 h after meal, mean at each time point, mean incremental value after meal, and changes from baseline will be summarized using descriptive statistics by treatment group. Seven-point mean model-fitting analysis will be performed.

7.3.3 Subgroup Analyses

The following subgroups will be analyzed:

- Age (< 65 years; ≥ 65 years)
- Gender (M/F)
- Baseline Weight (< 75 kg; ≥ 75 kg)
- Baseline BMI (< 28 kg/m², ≥ 28 kg/m²)
- Baseline HbA_{1c} ($< 8.5\%$, $\geq 8.5\%$)
- Baseline eGFR (< 60 mL/min/1.73m², ≥ 60 mL/min/1.73m²)
- Diabetes mellitus Course of disease (≤ 5 years, > 5 to ≤ 10 years, > 10 years)
- Hypertension (combined, not combined)
- Dyslipidaemia (combined, not combined)
- Fatty liver (combined, not combined)
- Hepatic function abnormal (combined, not combined)
- Hyperuricaemia (combined, not combined)

The MMRM model will be used at the level of each subgroup factor. The treatment group, visit, treatment group-by-visit interaction, randomization stratification factors (randomization stratification factors are the HbA_{1c} level before randomization (V3), so randomization stratification factors are not considered as fixed effects in the corresponding subgroup analysis), as fixed effects, and the baseline value of the indicator will be used as covariates for model fitting analysis. The difference in efficacy between the two IBI362 dose groups and the placebo group and its 95% CI in each subgroup level will be calculated. In addition, subgroup factor, treatment group, visit, randomization stratification factor, interaction term between treatment group and visit, interaction term between visit and subgroup factor, interaction term between treatment group, visit and subgroup factor, and interaction term between

subgroup factor and treatment group will be included as fixed effects, and the baseline value of the indicator will be used as a covariate in the full model fitting analysis to provide the p value of interaction term between subgroup factor and treatment group. If the number of participants in a subgroup factor was too small, the subgroup would not be analyzed. The indicators analyzed were:

- Change from baseline in HbA_{1c} at Week 24
- Percent Change from Baseline in Body Weight at Week 24

The response of corresponding parameters will also be summarized separately for participants with hypertension, dyslipidemia, abnormal liver function, and hyperuricemia:

- Change in blood uric acid from baseline at each visit in participants with hyperuricemia
- Changes in TC, LDL-C, and TG from baseline at each visit in participants with dyslipidemia
- Changes in ALT and AST from baseline at each visit for participants with abnormal liver function
- Changes in systolic and diastolic blood pressures from baseline at each visit in participants with hypertension
- Changes in blood uric acid from baseline at each visit for participants with baseline blood uric acid ≥ 420 $\mu\text{mol/L}$
- Changes in TG from baseline at each visit for participants with baseline TG ≥ 1.7 mmol/L
- Changes in TC from baseline at each visit for participants with baseline TC ≥ 5.2 mmol/L
- Changes in LDL-C relative to baseline at each visit for participants with baseline LDL-C ≥ 3.4 mmol/L

7.3.4 Quality of life improvement questionnaire

DTSQ Questionnaire

In the modified intention-to-treat (mITT) analysis set, data will be summarized descriptively by self-perceived hyperglycemia (DTSQ Question 2 score), self-perceived hypoglycemia (DTSQ

Question 3 score), and overall treatment satisfaction (DTSQ Question 1 and sum of scores of Questions 4-8).

EQ - 5D- 5L Questionnaire

In the modified intention-to-treat (mITT) analysis set, data were summarized descriptively by mobility, self-care, usual activities, pain/discomfort, anxiety/depression (5-level classification), and health status (0-100 domain score) for the day.

Data of individual participants will be tabulated.

7.3.5 Multiplicity Issues

Under the analysis framework of the treatment-policy estimand and the efficacy estimand, the statistical superiority of the two IBI362 dose groups over the placebo group in the primary and key secondary endpoints will be adjusted for multiplicity using the sequential hierarchical testing strategy, respectively. No multiplicity adjustment will be performed between the two estimands.

The order of testing for the primary and key secondary endpoints is:

- 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 Weight decrease by $\geq 5\%$ from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Proportion of participants with HbA_{1c} < 7.0% and Weight decrease by $\geq 5\%$ from baseline at week 24 (IBI362 4.0 mg vs. placebo);
- Proportion of participants whose Weight decreased by $\geq 5\%$ from baseline at Week 24 (IBI362 6.0 mg vs. placebo);
- Proportion of participants whose Weight decreased by $\geq 5\%$ from baseline at Week 24 (IBI362 4.0 mg vs. placebo);
- Percentage change in Weight from baseline at week 24 (IBI362 6.0 mg vs. placebo);
- Percentage change in Weight from baseline at week 24 (IBI362 4.0 mg vs. placebo).

The IBI362 dose groups will be sequentially compared with the placebo group for efficacy differences at each endpoint. If the endpoint is statistically significant ($p < 0.05$), then the IBI362 dose

group can be considered statistically superior to the placebo group at that endpoint, and the comparison for the next endpoint can be conducted. If the comparison result is not significant ($p \geq 0.05$), then it is considered that the IBI362 dose group is not statistically superior to the placebo group in terms of this endpoint, and the between-group comparison of any endpoint after this endpoint sequence will not be conducted.

All between-group comparisons were performed in parallel at the level of $\alpha = 0.05$ for both estimands. At the time of marketing registration application, the efficacy analysis will be mainly based on the treatment-policy estimand, and the IBI362 group will be considered superior to the placebo group when the primary endpoint is reached based on the treatment-policy estimand. The efficacy estimand is only used as supporting evidence. Other non-registration purposes, such as publication of articles, will be mainly based on the efficacy estimand, and when the primary endpoint under the efficacy estimand is reached, the IBI362 group will be considered superior to the placebo group. Since the clinical questions answered by the two estimands and the application objectives of the two estimands were different, no multiplicity adjustment was performed between the two estimands.

7.4 Extent of Study Drug Exposure and Compliance

The extent of exposure and compliance of the investigational drug will be analyzed based on the safety set (SS).

Days of Exposure

Days of exposure = Date of last dose – Date of first dose + 7 days

Weeks of Exposure

Weeks of exposure = Days of exposure/7, rounded to one decimal place.

The number of days and weeks of study drug exposure of participants during the study will be descriptively summarized by treatment group and treatment period (double-blind treatment period of IBI362 group and placebo group, overall treatment period of IBI362 group, and extension period of placebo group).

The number of weeks of drug exposure in the study will be summarized by the following categories (rounded up):

- > 0 week
- ≥ 4 weeks
- ≥ 8 weeks
- ≥ 12 weeks
- ≥ 16 weeks

-
- ≥ 20 weeks
 - ≥ 24 weeks

For the overall treatment period of the IBI362 group, the following categories will also be summarized:

- ≥ 28 weeks
- ≥ 32 weeks
- ≥ 36 weeks
- ≥ 40 weeks
- ≥ 44 weeks
- ≥ 48 weeks

Number of doses

The number of study drugs used by the participants during the study will be descriptively summarized by treatment group and treatment period (double-blind treatment period of IBI362 group and placebo group, overall treatment period of IBI362 group, and extension period of placebo group).

The total number of actual doses received by participants in the study will be summarized according to the following categories:

- > 0 times
- ≥ 4 times
- ≥ 8 times
- ≥ 12 times
- ≥ 16 times
- ≥ 20 times
- ≥ 24 times

For the overall treatment period of the IBI362 group, the following categories will also be summarized:

- ≥ 28 times
- ≥ 32 times
- ≥ 36 times
- ≥ 40 times
- ≥ 44 times
- $= 48$ times

Dose modification

Missing or interrupted study drugs and reasons for non-resumption during the study will be summarized by treatment group and treatment period (double-blind treatment period for IBI362 groups and placebo group, overall treatment period for IBI362 groups, and extension period for placebo group).

The number and percentage of participants who received the starting dose, the second dose, and the third dose by week were summarized by group, and the last dose of the study drug was summarized for all participants and participants who prematurely discontinued the study drug.

Drug Compliance

Drug compliance (%) = (cumulative number of vials used/cumulative number of vials planned to be administered) × 100%

The cumulative planned number of vials will be calculated based on the planned number of vials from the start of the first dose to the date of the last dose. Among them, the records collected in the CRF with reasons for not receiving the study drug treatment, including "adverse event", "COVID-19 infection/suspected COVID-19 infection", "affected by COVID-19", and "pregnancy" among "other" reasons, will not be included in the planned number of vials. The calculation of the cumulative number of vials of the drug is based on the actual number of vials of the investigational product used.

Drug compliance will be summarized by treatment group and trial stage (double-blind treatment period for IBI362 group and placebo group, overall treatment period for IBI362 group, and extension period for placebo group).

The exposure of medications of participants will be listed. Drug use errors will also be tabulated.

7.5 Safety analysis

The safety analysis will be based on the safety analysis set by actual treatment.

7.5.1 Adverse Events

Adverse events are classified into the following categories according to the date of onset:

Pre-treatment AEs: AEs that occur from the signing of the informed consent form to before the first dose of the study drug.

Treatment-emergent adverse events (TEAEs): AEs that occurred or worsened from the start of the first study dose to 56 days after the last dose.

TEAEs in the double-blind treatment period were defined as AEs that occurred or worsened from the start of the first dose of the study drug to before the first dose of the drug in the extension period of the study.

TEAEs during the extension period of the study are defined as AEs that occurred or worsened from the start of the first dose of study drug during the extension period to within + 56 days after the last dose.

Post-treatment period AEs: AEs that occur after the last dose + 56 days.

If the start date/time of an AE is completely/partially missing, the pre-treatment/treatment-emergent AE will be marked according to the rules in [Section 6.3](#).

Treatment-emergent adverse event

The incidence of the following AEs will be summarized by group. For all categories of TEAEs, the TEAEs during the double-blind treatment period in the IBI362 group and the placebo group, the TEAEs during the overall treatment period in the IBI362 group, and the TEAEs during the extension period in the placebo group will be summarized separately:

- All adverse events
- Pre-Treatment Adverse event
- Treatment-emergent Adverse event (TEAE)
- Severe TEAEs
- Treatment-related Adverse event (TRAEs)
- Severe TRAEs
- Serious treatment-emergent Adverse event (SAE)
- Study drug-related treatment-emergent SAEs (TRSAEs)
- TEAE Leading to Death
- TRAE Leading to Death
- TEAE Leading to Study Drug Discontinuation
- TRAE Leading to Study Drug Discontinuation
- TEAE Leading to Study Drug Interruption
- TRAE Leading to Study Drug Interruption
- Treatment-emergent AESIs
 - Severe gastrointestinal reactions (Nausea, Vomiting, Diarrhoea)
 - Hypoglycaemia Event
 - Pancreatitis acute
 - Thyroids Neoplasm malignant and Thyroid C Cells Hyperplasia
 - Major Cardiovascular Events
 - Supraventricular tachycardia and Conduction Block

-
- Anaphylaxis and Injection site reaction
 - Diabetes mellitus Retinopathy Complications
 - Acute kidney injury
 - Acute gallbladder disease
 - Severe AESIs
 - AESIs related to the study drug
 - Treatment-emergent Gastrointestinal disorders
 - Post-treatment Adverse event

The following TEAEs were summarized by treatment group and treatment period (double-blind treatment period for IBI362 groups and placebo group, overall treatment period for IBI362 groups, and extension period for placebo group):

Adverse event will be summarized by MedDRA SOC, PT, and maximum severity (mild < moderate < severe):

- TEAE(s)
- TRAEs
- AESI
- SAEs
- Treatment-emergent Gastrointestinal disorders: Defined as the treatment period Adverse event with the preferred system organ class of " Gastrointestinal disorders ".
See [Appendix 5](#) for detailed derive rules.
- Treatment-emergent Gastrointestinal disorders in Participants Who Discontinued Study Drug Prematurely

The number of participants, percentage, number of events, and event rate per 100 person-years in the following categories Adverse event will be summarized by MedDRA SOC and PT, respectively:

- AESI
- Treatment-emergent Gastrointestinal disorders

The summary of the above AE categories will be sorted in descending order of the total incidence of AEs.

The duration of the following categories Adverse event will be summarized by SOC and PT coded by MedDRA:

- Treatment-emergent SAEs
- Study drug-related treatment-emergent SAEs
- TEAEs leading to discontinuation of study drug

-
- TEAEs leading to interruption of investigational drug
 - AESI
 - Treatment-emergent Gastrointestinal disorders
 - Treatment-emergent Gastrointestinal disorders in Participants Who Discontinued Study Drug Prematurely

The time from the first dose of the investigational product to the first occurrence of the following AEs will be summarized by MedDRA SOC and PT Adverse event . The number of participants with corresponding events will also be summarized by ≤ 4 weeks, $4 \leq 8$ weeks, $8 \leq 12$ weeks, and > 12 weeks. Kaplan Meier curves will also be plotted for Adverse event below.

- Treatment-emergent SAEs
- Study drug-related treatment-emergent SAEs
- TEAEs leading to discontinuation of study drug
- TEAEs leading to interruption of investigational drug
- AESI
- Treatment-emergent Gastrointestinal disorders

Listings will also be provided for the following Adverse event . The listing should include at least the group, participant number, date of first dose, start date, end date, severity, relationship with the drug, action taken, outcome, and other information of the AE.

- All Adverse event
- TEAEs leading to discontinuation of study drug
- TEAEs leading to interruption of investigational drug
- Severe TEAEs
- AESI
- SAEs
- TEAEs leading to Death

Hypoglycaemia Event

Among the participants with Hypoglycaemia events collected in the CRF, the Hypoglycaemia events occurring in the study will be summarized by treatment group and treatment stage (double-blind treatment period of IBI362 group and placebo group, overall treatment period of IBI362 group, and extension period of placebo group).

According to the American Diabetes mellitus Association (ADA)/European Diabetes mellitus Association for the Study of Diseases (EASD) (2017) Hypoglycaemia classification criteria, Hypoglycaemia is defined as follows:

- Hypoglycaemia A warning level is reached (level 1) and the plasma glucose concentration is not higher than 70 mg/dL (3.9 mmol/L)
 - Symptomatic Hypoglycaemia: plasma glucose not above 70 mg/dL (3.9 mmol/L) but above or equal to 54 mg/dL (3.0 mmol/L) with associated Hypoglycaemia symptoms.
 - Asymptomatic Hypoglycaemia: The plasma glucose concentration is not higher than 70 mg/dL (3.9 mmol/L) but is greater than or equal to 54 mg/dL (3.0 mmol/L) without Hypoglycaemia related symptoms.
 - Unclassified Hypoglycaemia: plasma glucose concentration no higher than 70 mg/dL (3.9 mmol/L) but greater than or equal to 54 mg/dL (3.0 mmol/L) with no Hypoglycaemia record of symptom-related information.
- Clinically Significant Hypoglycaemia (Grade 2), plasma glucose concentration not higher than 54 mg/dL (3.0 mmol/L)
 - Symptomatic Hypoglycaemia: Plasma glucose concentration $\leq$ 54 mg/dL (3.0 mmol/L) with symptoms related to Hypoglycaemia .
 - Asymptomatic Hypoglycaemia: Plasma glucose concentration $\leq$ 54 mg/dL (3.0 mmol/L) without Hypoglycaemia symptoms.
 - Unclassified Hypoglycaemia: plasma glucose concentration not above 54 mg/dL (3.0 mmol/L) without Hypoglycaemia documented symptom-related information.
- Severe Hypoglycaemia (Grade 3)
- Night Hypoglycaemia (Start Time 0am - 6am)

All Hypoglycaemia events and Hypoglycaemia events occurring before the addition of other hypoglycemic drugs will be summarized separately. The IBI362 dose level at which the Hypoglycaemia event occurs will also be summarized. Provide Hypoglycaemia event listings.

Rescue treatment

In the safety analysis set, participants are summarized and listed by treatment group and trial stage (double-blind treatment period of IBI362 group and placebo group, overall treatment period of IBI362 group, and extension period of study of placebo group) for whether they meet the Diabetes mellitus

rescue treatment criteria specified in the protocol, whether they have received rescue treatment, the time from the first dose of IMP to the first dose of rescue treatment, and the drugs used in the treatment.

Death

The Death and Death reasons occurring in the study will be summarized by treatment group and treatment stage (double-blind treatment period of IBI362 group and placebo group, overall treatment period of IBI362 group, and extension period of placebo group).

A listing of all occurrences Death during the study will also be provided. The listing should at least include group, participant number, date of first dose, Death date, Death reason, etc.

Depression /Suicidal Ideation

See [Appendix 5](#) for specific derive rules.

The treatment period related to Depression /suicidal ideation Adverse event will be summarized by MedDRA SMQ and PT respectively by treatment group and treatment phase (double-blind treatment period for IBI362 group and placebo group, overall treatment period for IBI362 group, and extension period for placebo group).

7.5.2 Laboratory Investigation

Laboratory test Including hematology, blood biochemistry, and urinalysis. The specific parameters tested in the local laboratory are shown in the table below:

Category	Parameter
Blood routine	Red blood cell count (Red Blood Cell, RBC), White blood cell count (White Blood Cell, WBC), Platelet (PLT), Haemoglobin concentration, hematocrit (HCT), Differential white blood cell count (Neutrophils, Basophils, Eosinophils, Monocytes and Lymphocytes)
Blood biochemistry	Aspartate aminotransferase Aspartate aminotransferase (AST), Alanine aminotransferase alanine aminotransferase (ALT), total bilirubin (TBIL), direct bilirubin (DBIL), albumin (ALB), Protein total total protein (TP), Ammonia gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH); Serum potassium, serum sodium, serum calcium, and serum chloride; Uric acid (UA), urea or urea nitrogen, creatinine (Cr), and creatine kinase (CK)
Blood Lipids	Total cholesterol (TC), triglyceride (TG), High density lipoprotein high-density lipoprotein cholesterol (HDL-C), Low density lipoprotein low-density lipoprotein cholesterol (LDL-C)
Routine urine test	Urine pH, Protein urine protein (UPRO), Glucose urine glucose (UGLU), Urine ketone body, Red blood cells urine red blood cell (URBC), White blood cells urine urinary white blood cell (UWBC)
Other Investigation	Calcitonin, Blood Amylase, Blood Lipase

Viral serology	Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), hepatitis B core antibody (HBcAb), HCV antibody, HIV antibody, Syphilis antibody
Thyroid Function	Thyroid stimulating hormone (TSH), free triiodothyronine Ammonia (FT3), and Thyroxine free (FT4)

The specific indicators tested at the central laboratory are shown in the table below:

Category	Parameter
Blood biochemistry	ALT, AST, uric acid, and creatinine
Blood Lipids	TC, TG, HDL-C, LDL-C
Other Investigation	Blood Amylase, Blood Lipase, Calcitonin, Fasting Insulin, Fasting C-peptide, Serum 1,5-Dehydration Glucotrol (1,5-AG)

The blood biochemistry parameters (ALT, AST, and uric acid), blood lipid parameters (TC, TG, HDL-C, and LDL-C), fasting insulin, fasting C-peptide, and 1,5-AG measured in the central laboratory, as well as fasting plasma glucose, Glycosylated haemoglobin, and Albumin urine /creatinine ratio, will only be analyzed for potentially clinically significant abnormal values in the safety analysis section (if involved). The statistical descriptive analysis and model fitting analysis will be presented in the efficacy section. The analyses of creatinine (and its calculated eGFR), blood Amylase, blood Lipase, calcitonin, Albumin urine, and Creatinine urine were the same as the analyses of other safety endpoints.

Changes in blood biochemistry, blood routine, and blood lipids from baseline at each visit will be summarized by group. The normal and abnormal results with or without clinical significance at baseline of each Laboratory test (blood biochemistry, blood routine, urine routine, blood lipids, serum calcitonin, blood Amylase and blood Lipase) will be summarized by group and treatment stage. The potential clinically significant abnormal values of the parameters will also be summarized by treatment group and treatment period (double-blind treatment period for IBI362 groups and placebo group, overall treatment period for IBI362 groups, and extension period for placebo group) according to [Appendix 4 Laboratory test](#) . The results of Laboratory test will be listed.

7.5.3 Vital Signs

Vital signs include Body temperature, pulse, and blood pressure (systolic blood pressure and diastolic blood pressure).

Vital signs at each visit and their changes from baseline will be summarized by group. Line charts of pulse rate and its change from baseline at each visit will be provided.

The potentially clinically significant vital sign parameters will also be summarized by treatment group and treatment period (double-blind treatment period for IBI362 groups and placebo group,

overall treatment period for IBI362 groups, and extension period for placebo group) according to [Appendix 4](#).

The results of vital signs will be listed.

7.5.4 Electrocardiogram

The ECG parameters to be analyzed are heart rate (HR), RR interval, QT interval, QTcF and PR interval.

The results of 12-lead ECG and their changes from baseline will be summarized at each evaluation time point. The normal and clinically significant abnormal 12-lead ECG results before and after baseline were summarized by group and study stage.

The potential clinically significant ECG parameters will also be summarized by treatment group and treatment period (double-blind treatment period for IBI362 groups and placebo group, overall treatment period for IBI362 groups, and extension period for placebo group) according to [Appendix 4](#).

The ECG test results will be listed.

7.5.5 Physical Examination

Physical examination visits will be summarized using descriptive statistics.

A listing of all physical examination findings for each participant will also be provided.

7.6 Immunogenicity Analysis

In the SS, the positive rates and titers of anti-drug antibody (ADA) and neutralizing antibody (NAb) as well as the immunogenicity test results at each assessment time point will be summarized by IBI362 dose group.

The antibody levels of participants will be tabulated.

In addition, the following contents will be summarized separately for ADA-positive and ADA-negative participants during the treatment period:

- Overview of Adverse Events
- Change in HbA_{1c} from baseline by visit

7.7 Pharmacokinetic Analysis

For detailed PK analysis, please refer to the PK analysis plan.

7.8 Analysis Plan and Data Monitoring Meeting

After the last participant completed the week 24 visit and the database was frozen, the PopPK/PD data were analyzed by a pre-specified independent PopPK/PD data analysis team. Refer to "Procedures for Maintaining the Blind in the PopPK/PD Analysis of CIBI362A301" for details of the blinding maintenance process. In addition to the pre-specified independent PopPK/PD data analysis team members, other sponsor personnel, investigators, and participants will continue to maintain the blind.

The final analysis of the study will be performed after the last participant completes the Week 52 safety follow-up and the final database is locked.

There were no scheduled data monitoring meetings for this trial.

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APPENDICES

Appendix 1 Schedule of Activities

Table 4. Schedule of Activities

	Screening Period ¹	Run-in period		Double-blind treatment period								Study Extension Period					Safety follow- up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V 1	V 2	V 3	V 4	V5	V6	V 7	V 8	V9	V 10	V11	V 12	V 13	V 14	V 15	V 16	V 17	
Visit time (week, W)	-10 to -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 Informed Consent Form	X																	
Assignment of screening number	X																	
Inclusion / Exclusion Criteria Assessment	X																	

STATISTICAL ANALYSIS PLAN

Innovent Biologics (Suzhou Co., Ltd.)

Version No. : v 1.0

CIBI362 A 301

Version Date: April - 10 - 2024

	Screening Period ¹	Run-in period		Double-blind treatment period								Study Extension Period					Safety follow- up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V 1	V 2	V 3	V 4	V5	V6	V 7	V 8	V9	V 10	V11	V 12	V 13	V 14	V 15	V 16	V 17	
Visit time (week, W)	-10 to -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																	
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

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	Screening Period ¹	Run-in period	Double-blind treatment period									Study Extension Period					Safety follow- up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V 1	V 2	V 3	V 4	V5	V6	V 7	V 8	V9	V 10	V11	V 12	V 13	V 14	V 15	V 16	V 17	
Visit time (week, W)	-10 to -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	
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			
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,		X																

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Study Visit	V 1	V 2	V 3	V 4	V5	V6	V 7	V 8	V9	V 10	V11	V 12	V 13	V 14	V 15	V 16	V 17	
Visit time (week, W)	-10 to -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	
SMBG training, and self-injection training																		
Distribution of diary cards		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
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		

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Study Visit	V 1	V 2	V 3	V 4	V5	V6	V 7	V 8	V9	V 10	V11	V 12	V 13	V 14	V 15	V 16	V 17	
Visit time (week, W)	-10 to -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 investigational 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
HbA _{1c} ¹³	X		X	●		●		●		●	●	●		●	●	●		●

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Study Visit	V 1	V 2	V 3	V 4	V5	V6	V 7	V 8	V9	V 10	V11	V 12	V 13	V 14	V 15	V 16	V 17	
Visit time (week, W)	-10 to -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	
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				●						●		●				●		●
eGFR (CKD-EPI) ¹⁹	X			●						●		●				●		●
Viral serological testing ²⁰	X																	

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	Screening Period ¹	Run-in period	Double-blind treatment period									Study Extension Period					Safety follow- up period	Premature discontinuation of treatment/withdrawal from the study ²
Study Visit	V 1	V 2	V 3	V 4	V5	V6	V 7	V 8	V9	V 10	V11	V 12	V 13	V 14	V 15	V 16	V 17	
Visit time (week, W)	-10 to -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	
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

Remarks:

- If the screening examinations are more than 14 days from the run-in date, HbA_{1c}, vital signs, hematology, blood biochemistry, blood lipids, urinalysis, ECG, amylase, lipase, calcitonin, thyroid function, and serum pregnancy tests should be repeated.
- 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 of the protocol. If the

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- 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 of the protocol), and only participants who meet the criteria can enter the subsequent trial process. Participants who do not meet the criteria will be treated as run-in failures. The duration of the run-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 run-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 run-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: Complete before administration (except for visits without administration). Blood pressure and pulse should be measured twice on the same arm, and after the end of the first blood pressure measurement, they should be measured again after an interval of 1 min. See Section 6.2.2.2 of the protocol 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) Standing position, relax both shoulders and abdomen, breathe steadily, and separate feet by 25-30 cm; (2) Horizontal position of measurement: the midpoint of the line connecting the anterior superior iliac spine on the midaxillary line and the lower edge of the 12th rib; (3) Use a tape measure to wrap around the abdomen at the above horizontal position, and the tape measure should be close to the skin, but should not strangulate the skin; (4) When measuring, do not consciously retract or stiffen the abdomen, and read at the end of calm expiration. The unit of waist circumference is cm, rounded to 1 decimal place (such as: 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, the 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

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- non-consecutive days should be collected. At least one complete seven-point fingertip blood glucose measurement 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. Administer 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, the investigator may also perform additional blood/urine tests based on clinical judgment Pregnancy test .
 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. Refer to the central laboratory manual for detailed procedures. 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. Refer to the central laboratory manual for detailed procedures.
 16. Local Laboratory test includes:
 - (1) Hematology: White blood cell count, Red blood cell count, platelets, Haemoglobin concentration, hematocrit, Differential white blood cell count (neutrophils, basophils, eosinophils, monocytes, and lymphocytes);
 - (2) Blood biochemistry: ALT, AST, total bilirubin, direct bilirubin, albumin, Protein total, Ammonia 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: total cholesterol (TC), triglyceride (TG), High density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL-C);
 - (4) Blood Amylase and blood Lipase (at least blood Amylase tests are required if the study site is limited in availability);
 - (5) Urinalysis: Urine pH, Protein urine, Glucose urine, Urine ketone body, Red blood cells urine, and White blood cells urine;
 - (6) Calcitonin (If calcitonin cannot be detected due to the limited conditions of the study site, options include: 1) calcitonin in other participating study sites of CIBI362A301 in the same city Investigation; 2) calcitonin in a tertiary hospital other than the participating study site of CIBI362 A301 in the same city Investigation).
 17. The blood collection points at the site 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:

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- (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 of the protocol), and the results were recorded rounded to 1 decimal place.
 20. Virus serology test: including human immunodeficiency virus (HIV) antibody, hepatitis B test (HBsAg, HBsAb, HBcAb, HBcAg, 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 h $\pm$ 1 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.

Appendix 2. Classification and Derive Rules of Comorbidities at Baseline.

Classification	Filter Criteria
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Hypertension	PT: hypertension
Dyslipidaemia	PTs: hyperlipidemia, hypertriglyceridemia, dyslipidemia, low HDL cholesterolemia, hypercholesterolemia
Fatty liver	PTs: hepatic steatosis, nonalcoholic fatty liver disease, steatohepatitis
Hyperuricemia/gout	PTs: hyperuricemia, gout
Hepatic function abnormal	PTs: hepatic function abnormal, liver injury, alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hypertransaminasaemia

Screening was performed for ongoing medical history and pretreatment adverse events.

Appendix 3. Classification and Derive Rules for Diabetic Complications at Baseline

Classification	Filter Criteria
Retinopathy	PTs: amaurosis, Amaurosis fugax, arteriosclerotic retinopathy, blindness, Blindness transient, Blindness unilateral, choroidal neovascularization, cystoid macular edema, Detachment of macular retinal pigment epithelium, Detachment of retinal pigment epithelium, diabetic blindness, diabetic eye disease, diabetic retinal edema, diabetic retinopathy, diabetic uveitis, diplopia, exudative retinopathy, ocular laser surgery, fundoscopy, fundoscopy abnormal, Intra-ocular injection, macular detachment, macular edema, maculopathy, noninfective chorioretinitis, noninfective retinitis, Phacotrabeculectomy, retinal aneurysm, retinal arteriovenous malformation, Retinal artery embolism, Retinal artery occlusion, retinal artery stenosis, Retinal collateral vessels, Retinal cryoablation, retinal detachment, retinal exudates, Retinal haemorrhage, Retinal laser coagulation, retinal neovascularization, retinal edema, retinal surgery, retinal thickening, retinal vascular disease, retinal vascular occlusion, retinal vein occlusion, retinitis, retinopathy, Retinopathy haemorrhagic, hypertensive retinopathy, ultrahigh viscosity retinopathy, proliferative retinopathy, flash scotoma, Sudden visual loss, venous stasis retinopathy, blurred vision, visual impairment, Visual acuity reduced, Visual acuity reduced transiently, Vitrectomy
Neurological disorder	PTs: Neuropathy peripheral, Mononeuropathy, Autonomic neuropathy, Orthostatic hypotension, Diabetes mellitus Neuropathy, Diabetic mononeuropathy
Nephropathy	PT: Diabetes mellitus Nephropathy, Nephropathy Narrow scope terms of Acute renal failure SMQ (20000003) Chronic kidney disease Narrow scope terms of SMQ (20000213)

Screening is performed during ongoing medical history and pretreatment Adverse event .

Appendix 4. Criteria for Potentially Clinically Significant Abnormal Values (PCSA).

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Parameter	PCSA	Remarks
<i>Liver function parameters</i>	Refer to 2009 FDA " Technical Guidelines for Evaluation of Drug Hepatotoxicity "	
ALT	● $ALT \geq 3 \times ULN$ (baseline $ALT < ULN$), $ALT > 2 \times$ baseline (baseline $ALT \geq ULN$) ● $\geq 5 ULN$ ● $\geq 10 ULN$ ● $\geq 20 ULN$	
AST	● $AST \geq 3 \times ULN$ (baseline $AST < ULN$), $AST > 2 \times$ baseline (baseline $AST \geq ULN$) ● $\geq 5 ULN$ ● $\geq 10 ULN$ ● $\geq 20 ULN$	
ALP (Alkaline Phosphatase)	● $> 1.5 ULN$	
TBIL (total bilirubin)	● $> 1.5 ULN$ ● $> 2 ULN$	
DBIL (Direct Bilirubin)	● $> 35\% TBIL$ and $TBIL > 1.5 \times ULN$	
ALT + TBIL	● $ALT > 3 ULN$ and $TBIL > 2 ULN$	
<i>Renal function indicators</i>		
eGFR (Glomerular filtration rate, CKD-EPI formula, mL/min/1.73m ²)	● <15 (Terminal Phase Nephropathy) ● ≥ 15 to < 30 (severe GFR decrease) ● ≥ 30 to < 60 (moderate GFR decline) ● ≥ 60 to < 90 (mildly decreased GFR)	2017 "Chronic Kidney Disease Screening, Diagnosis and Prevention Guidelines", FDA draft Guidance 2010
Scr (Blood creatinine)	● $\geq 150 \mu\text{mol/L}$ (adults) ● $\geq 30\%$ (increase from baseline)	FDA draft guidance 2010

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	● $\geq 100\%$ (increase from baseline)	
UACR (Albumin urine creatinine ratio, mg/g)	● ≥ 30 to ≤ 300, and baseline < 30 ● > 300 and baseline < 30 ● > 300 and baseline ≥ 30 to ≤ 300	
Other blood biochemistry parameters		
ALB (Albumin)	● < 35 g/L ● < 30 g/L ● < 20 g/L	CTCAE v5.0
Electrolytes	● Blood chloride: < 80 mmol/L, > 115 mmol/L ● Blood sodium: ≤ 129 mmol/L, ≥ 160 mmol/L ● Blood potassium: < 3 mmol/L, ≥ 5.5 mmol/L ● Blood calcium: 3.1 mmol/L	FDA Feb 2005
Blood routine		
WBC (White blood cell count)	● $< 3.0 \times 10^9/L$, $\geq 16.0 \times 10^9/L$	
Lym (Lymphocyte count)	● $> 4.0 \times 10^9/L$, $< 0.8 \times 10^9/L$	
Neu (Neutrophil count)	● $< 1.5 \times 10^9/L$	International Consensus meeting on drug-induced blood cytokines, 1991. FDA Criteria.
Mono (Monocyte count)	● $> 0.7 \times 10^9/L$	
HBG (Haemoglobin)	● Mild Anaemia: > 90 g/L, ≤ 120 g/L (males), ≤ 110 g/L (females) ● Moderate Anaemia: 60-90 g/L ● Severe Anaemia: 30–59 g/L ● Serious Anaemia: < 30 g/L ● Decrease of ≥ 20 g/L from baseline	WHO Anaemia Diagnostic Criteria

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	● Decrease of ≥ 20 g/L from baseline, and Anaemia (≤ 120 g/L (male), ≤ 110 g/L (female)) ● Normal at baseline but during the study Anaemia (≤ 120 g/L (male), ≤ 110 g/L (female)) ● ≥ 185 g/L (male), ≥ 165 g/L (female)	
RBC (Red blood cell count)	● $\geq 6 \times 10^{12}/L$	
PLT (Platelet count)	● $< 100 \times 10^9/L$ ● $\geq 700 \times 10^9/L$	International Consensus meeting on drug-induced blood cytopenias, 1991.
Vital Signs		
Pulse	● < 50 bpm and with ≥ 20 bpm decrease from baseline ● < 40 bpm ● > 100 bpm and with ≥ 20 bpm increase from baseline ● > 100 bpm and with ≥ 20 bpm increase from baseline 2 consecutive visits ● > 100 bpm and with ≥ 20 bpm increase from baseline 3 consecutive visits ● > 120 bpm ● > 120 bpm for 2 consecutive visits ● > 120 bpm for 3 consecutive visits	
SBP (systolic blood pressure)	● ≤ 90 mm Hg and with ≥ 20 mm Hg decrease from baseline ● ≥ 160 mmHg with ≥ 20 mmHg increase from baseline	
DBP (diastolic blood pressure)	● ≤ 50 mmHg and decrease of ≥ 10 mmHg from baseline ● ≥ 110 mmHg with ≥ 10 mmHg increase from baseline	

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= <i>Electrocardiogram</i>	ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4): 489-500)	
HR (Heart rate)	● < 50 bpm and with ≥ 20 bpm decrease from baseline ● < 40 bpm ● >100 bpm and with ≥ 20 bpm increase from baseline ● >120 bpm	
PR Interval	● >200 msec and an increase of $\geq 25\%$ from baseline ● >220 msec ● >240 msec	
QT Interval	● >500 msec	
QTc Interval	● >450 msec ● >480 msec ● >500 msec ● Increase of 30-60 ms from baseline ● Increase from Baseline > 60 ms ● > 480 ms and with > 60 ms increase from baseline	
<i>Pancreatic enzymes</i>	American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis (2018)	
Blood Amylase	● > 3 ULN	
Blood Lipase	● > 3 ULN	
<i>Calcitonin</i>	● > 20 ng/L to ≤ 50 ng/L ● > 50 ng/L to ≤ 100 ng/L ● > 100 ng/L	Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma (2015)

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Appendix 5 Other Derive Rules

Classification	Code
Depression Disorder / Suicidal Ideation or Behavior	SMQ narrow terms 20000167, 20000037
Gastrointestinal disorders	SOC: 10017947

Note: The MedDRA coding version was 26.0.