Clinical Study Protocol

Study Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase II Clinical Study to Evaluate the Efficacy and Safety of HTD1801 in Type 2 Diabetes Mellitus (T2DM) Subjects

Protocol No.: HTD1801.PCT103

Version: Version 2.0

Date: 4/27/2022

Sponsor: Shenzhen HighTide Biopharmaceutical, Ltd.

Person in Charge from the Sponsor: Meng Yu

Contact Information of the Sponsor: 0755-21534843

Confidentiality Statement

Signature Page - Sponsor

I have read the full text of this protocol and agree to all the provisions listed herein.

I agree to:

- Conduct this study in strict accordance with the *Declaration of Helsinki,* Good Clinical Practice (GCP), relevant laws, regulations and guidelines, and this study protocol.
- Be responsible for the initiation, application, organization and funding of this clinical study, and to conduct audits on this clinical study.

Person in Charge from the Sponsor: Meng Yu

Signature Date

Signature Page - Investigator

I have read the full text of this protocol and agree to all the provisions listed herein.

I agree to:

- Earnestly fulfill the responsibilities as investigators according to the relevant regulations and guidelines including *Declaration of Helsinki,* Good Clinical Practice (GCP), Guidelines for Laboratory Management of Biological Samples Analysis in Drug Clinical Trials (Interim), etc.
- Make great efforts to strictly follow this protocol to conduct clinical studies.
- Keep all the data provided by the Sponsor in accordance with confidentiality requirements. When the data are to be submitted to the Ethics Committee, they must be marked as confidential.

Principal investigator: Prof. Linong Ji

Signature Date

Signature Page - Statistical Analysis Provider

I have read the full text of this protocol and agree to all the provisions listed herein.

I agree to:

- Earnestly fulfill the responsibilities as the statistical analyst according to the relevant regulations and guidelines including Good Clinical Practice (GCP), Technical Guidance for Clinical Trial Data Management, Technical Guidelines for Electronic Data Collection in Clinical Trials, Planning and Reporting Guidelines for Data Management and Statistical Analysis of Drug Clinical Trials, Guidelines for Biostatistics of Drug Clinical Trials, etc.
- Keep all the data provided by the Sponsor in accordance with confidentiality requirements.

Person in Charge from the Statistical Analysis Institution: Xian Yang

Signature Date

Signature Page - Phase II Study Institution

(Clinical Study Institution)

Protocol No.:	HTD1801.PCT103	**Protocol Version/Date:**	Version 2.0, 4/27/2022
Study Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase II Clinical Study to Evaluate the Efficacy and Safety of HTD1801 in Type 2 Diabetes Mellitus (T2DM) Subjects		
Institution No.:		**Investigator:**	
Study Institution:			

We have read and confirmed this protocol (Version 2.0, 4/27/2022. We agree to fulfill relevant responsibilities and conduct clinical studies in accordance with the *Declaration of Helsinki,* Good Clinical Practice (GCP), relevant laws and regulations, and this study protocol.

Investigator:

Signature Date

Protocol Amendment Record

Protocol/Amendment No.	Version No.	Version Date	Revised Contents
HTD1801.PCT103	1.0	11/23/2021	Not Applicable
HTD1801.PCT103	2.0	4/27/2022	Delete contents related to “GLP-1” collection and correct errors. Please see protocol amendment record for details.

Clinical Study Management Institution or Participants:

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PROTOCOL SYNOPSIS

Protocol No.	HTD1801.PCT103
Protocol Title	A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase II Clinical Study to Evaluate the Efficacy and Safety of HTD1801 in Type 2 Diabetes Mellitus (T2DM) Subjects
Version No.	2.0
Date	4/27/2022
Sponsor	Shenzhen Hightide Biopharmaceutical, Ltd.
Clinical Study Phase	Phase II
Indications	T2DM
Study Objectives	**Primary Objective:** 1. To evaluate the effect of HTD1801 on glycemic control in T2DM patients. **Secondary Objectives:** 1. To evaluate the safety of HTD1801 in T2DM patients. 2. To evaluate the effect of HTD1801 on improving insulin resistance (IR). 3. To evaluate the effect of HTD1801 on fatty liver-related indicators such as liver fat, alanine aminotransferase (ALT), aspartate aminotransferase (AST), etc. 4. To evaluate the effect of HTD1801 on metabolism-related indicators such as body weight, blood lipids, etc. 5. To evaluate the population pharmacokinetics (PPK) profiles of multiple-dose of HTD1801 in T2DM patients, and to provide a reference for determination of the dose in follow-up clinical studies. 6. To evaluate the effect of multiple-dose of HTD1801 on the intestinal flora characteristics, and the possible pharmacological effects by acting on the intestinal flora.
Efficacy Endpoints	Primary Efficacy Endpoint: Changes in glycosylated hemoglobin (HbA1c) from baseline with 12-week treatment. Secondary Efficacy Endpoints: 1. Percentage of subjects with HbA1c < 6.5% at Week 8 and 12. 2. Percentage of subjects with HbA1c < 7% at Week 8 and 12. 3. Changes in fasting blood glucose from baseline at Week 4, 8, and 12. 4. Changes in postprandial blood glucose from baseline at Week 8 and 12. 5. Changes in fasting insulin level from baseline at Week 4, 8, and 12. 6. Changes in postprandial insulin level from baseline at Week 8 and 12. 7. Changes in fasting C-peptide from baseline at Week 4, 8, and 12. 8. Changes in postprandial C-peptide from baseline at Week 8 and 12. 9. Changes in serum ALT, AST, gamma-glutamyl transpeptidase (GGT), and total bilirubin (TBIL) from baseline at Week 4, 8, and 12. 10. Changes in controlled attenuation parameter (CAP) measured by liver transient elastography from baseline with 12-week treatment. 11. Changes in C-reactive protein from baseline with 12-week treatment. 12. Changes in serum low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), total cholesterol (TC) from baseline at Week 4, 8, and 12. 13. Changes in body weights of subjects from baseline at Week 4, 8, and 12. 14. Changes in medication for blood lipid control in subjects from baseline with 12-week treatment. 15. Evaluation on the PPK parameters of multiple-dose of HTD1801 in T2DM patients. 16. Changes in characteristics of intestinal flora from baseline at Week 8 and 12. 17. Changes in characteristics of intestinal flora metabolites from baseline at Week 8 and 12.
Safety Indicators	Safety indicators include adverse events (AEs), hypoglycemia events, clinical laboratory tests (blood biochemistry, hematology, urinalysis and coagulation tests), 12-lead electrocardiogram (ECG), vital signs (body temperature, pulse and blood

<table>
<tr><td></td><td>pressure), physical examination, etc.</td></tr>
<tr><td>Study Design</td><td>This is a multicenter, randomized, double-blind, placebo-controlled, proof-of-concept and dose-range finding Phase II clinical study to evaluate the efficacy and safety of 12-week treatment with HTD1801 in T2DM patients.
In this study, 99 subjects are planned to be enrolled and randomized into the investigational drug low-dose group (HTD1801 500 mg, twice a day [BID]) , high-dose group (HTD1801 1000 mg, BID) and the placebo group at a ratio of 1:1:1, with 33 subjects in each group. The random stratification factors are CAP and HbA1c, and the random stratification will be conducted based on 1) HbA1c<8.5% and CAP<274 dB/m; 2) HbA1c<8.5% and CAP≥274 dB/m; 3) HbA1c≥8.5% and CAP<274 dB; 4) HbA1c≥8.5% and CAP≥274 dB/m.
Each subject should be included in the study for up to 22 weeks, including a screening phase of up to 2 weeks (14 days), a 4-week (28-day) single-blind introduction period, a 12-week (84-day) double-blind treatment phase, and a 4-week (28-day) safety follow-up visit phase of after the last dose.
<table>
<tr><td>Screening Phase (up to 2 weeks)</td><td colspan="2">Single-blind Introduction Period (4 weeks)</td><td colspan="2">Double-blind Treatment Phase (12 weeks)</td><td>Safety Follow-up Visit Phase (4 weeks after last dose)</td></tr>
<tr><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3"></td><td rowspan="2">Dose Group</td><td>HTD1801 500 mg, BID (N=33)</td><td></td></tr>
<tr><td>HTD1801 1000 mg, BID (N=33)</td><td></td></tr>
<tr><td>Control Group</td><td>Placebo, BID (N=33)</td><td></td></tr>
<tr><td colspan="6">-6w -4w D-7 to -5 D1 4w 8w 12w 16w
V1 V2 V3 V4 V5 V6 V7 V8</td></tr>
</table></td></tr>
<tr><td>Number of Subjects</td><td>99 subjects</td></tr>
<tr><td>Number of Study Sites</td><td>About 14 sites</td></tr>
<tr><td>Study Duration</td><td>The study will include the following phases:
• Screening phase: up to 2 weeks
• Single-blind introduction period: 4 weeks
• Double-blind treatment phase: 12 weeks
• Safety follow-up visit phase: 4 weeks after last dose</td></tr>
<tr><td>Eligibility Criteria</td><td>Inclusion criteria: subjects who meet all the following criteria will be included in this study.
1. Male or female subjects who are 18 (inclusive) to 75 (inclusive) years old when signing the informed consent forms (ICFs).
2. Subjects who are diagnosed as T2DM according to the World Health Organization (WHO) criteria 1999.
3. Subjects who have received diet and exercise treatment for ≥8 weeks prior to screening.
4. Subjects whose HbA1c must meet the following criteria:
(1) HbA1c level at screening (V1): 7.5%≤HbA1c≤11.0% (local laboratory);
(2) HbA1c level prior to randomization (V3): 7.0%≤HbA1c≤10.5% (central laboratory).
5. Subjects whose fasting blood glucose must meet the following criteria:
(1) Fasting blood glucose level at screening (V1): <13.9 mmol/L (if the plasma glucose cannot be detected in the local laboratory, the serum glucose result can be accepted);
(2) Fasting plasma glucose (FPG) level prior to randomization (V3): <13.9 mmol/L (central laboratory)
6. At screening phase, the body mass index (BMI) is within the range of 18 kg/m^2</td></tr>
</table>

(inclusive) to 40 kg/m^2 (inclusive).

7. Subjects who agree to maintain the same dietary and exercise habits throughout the study, and are willing and able to properly use a home blood glucose meter for self-monitoring of blood glucose (SMBG) and record.
8. Subjects who are able to understand and willing to sign the written ICFs and comply with the study protocol.

Exclusion criteria: subjects who meet any one of the following criteria will be excluded from this study.

1. Subjects who have Type 1 diabetes mellitus (T1DM), or specific diabetes mellitus (such as diabetes mellitus due to pancreatic injury, Cushing's syndrome or acromegaly, etc.).
2. Subjects who have diabetic ketoacidosis or hyperosmolar hyperglycemic state within 6 months prior to screening.
3. Subjects who have proliferative retinopathy or macular degeneration, severe diabetic neuropathy, diabetic foot, or intermittent claudication within 6 months prior to screening which are unstable and require treatment.
4. Subjects who have the history of ≥2 episodes of Grade 3 hypoglycemia within 12 months prior to screening (see Section 3.3.1.1 for the definition of hypoglycemia).
5. Subjects who have any disease that may cause hemolysis or erythrocyte instability and affect the HbA1c test, such as hemolytic anemia, etc., at screening (V1).
6. Subjects who have the weight changes (gain or loss) ≥5% prior to randomization (V3) compared with those at screening (V1).
7. Subjects who have the liver stiffness measurement (LSM) >13.0 kPa measured by liver transient elastography at screening (V1).
8. Subjects who have used any chemical or traditional Chinese medicines containing ursodeoxycholic acid (UDCA) or berberine (BBR) within 4 weeks prior to screening.
9. Subjects who are known to be allergic to the active ingredients of the investigational drug (HTD1801, BBR, UDCA) or its excipients; or known to be allergic to the salvage therapy drug Empagliflozin or related excipients.
10. Subjects who have the history of drug abuse or dependence within 12 months prior to screening.
11. Subjects who have the refractory urinary tract or genital infection within 6 months prior to screening.
12. Subjects who have severe gastrointestinal diseases at screening (V1) that affect drug absorption, distribution, metabolism and excretion, including chronic gastrointestinal disease that causes recurrent diarrhea (such as irritable bowel syndrome, ulcerative colitis, Crohn's disease, etc.); or have undergone gastrointestinal surgery that affects drug absorption, such as gastrostomy, anastomosis, or intestinal resection.
13. Subjects who have used insulin or its analogs for more than 2 consecutive weeks within 12 months prior to screening (use of insulin or its analogs for hyperglycemia during pregnancy prior to screening is not within the scope of this limitation);
14. Subjects who have used ≥2 types of hypoglycemic drugs with different mechanisms for more than 8 weeks and within 12 months prior to screening (use of insulin or its analogs for hyperglycemia during pregnancy prior to screening is not within the scope of this limitation).
15. Subjects who have used any drugs that may affect blood glucose metabolism within 8 weeks prior to screening, such as hypoglycemic drugs (including traditional Chinese medicines indicated for hypoglycemic therapy), systemic glucocorticoids (except for inhalation, eye instillation, and topical skin drugs), growth hormone, non-selective β-receptor blockers (such as propranolol, etc.), thiazide diuretics at a dose of >25 mg/day or aspirin at a dose of >300 mg/day, etc.
16. Subjects who have used liver-protecting drugs (including traditional Chinese medicine) or dietary supplements within 4 weeks prior to screening (see APPENDIX 1).

17. Subjects who have used any chemical drugs, traditional Chinese medicines or dietary supplements for weight loss (see APPENDIX 2), participated in a weight loss program, or followed a special diet within 4 weeks prior to screening.
18. Subjects who have used antibiotics (except for topical application) within 4 weeks prior to screening.
19. Subjects who have been administered with probiotic-containing drugs or dietary supplements within 4 weeks prior to screening or prior to randomization (V3) (see APPENDIX 3).
20. Subjects who have used lipid-lowering drugs at stable doses < 4 weeks at screening (V1) (see APPENDIX 4).
21. Subjects who have uncontrolled hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg) at screening (V1) or prior to randomization (V3).
22. Subjects who have abnormal thyroid function that cannot be controlled with drugs at stable doses, or clinically significant abnormality in thyroid function test results that requires drug treatment at screening (V1).
23. Subjects who have suffered from severe infection (such as acute pancreatitis, COVID-19) or severe trauma, or have undergone major surgery within 3 months prior to screening and are judged to be inappropriate to participate in this study by the investigator.
24. Subjects who have the history of the following acute or chronic liver diseases at screening (V1): autoimmune hepatitis, primary biliary cholangitis, alcoholic liver disease, hepatolenticular degeneration, or drug-induced liver injury.
25. Subjects who have the history of malignant tumors within 5 years prior to screening (except for cured basal cell carcinoma of the skin, carcinoma cervix in situ), or being assessed for potential malignant tumors at screening (V1).
26. Subjects who have the history of psychiatric diseases or are receiving drug treatment, and are judged to be inappropriate to participate in this study by the investigator at screening (V1).
27. Subjects who have the following history within 12 months prior to screening: decompensated heart failure (New York Heart Association [NYHA] Class III or IV), unstable angina, myocardial infarction, percutaneous coronary intervention, coronary bypass transplantation, hemorrhagic stroke, and ischemic stroke (except lacunar infarction).
28. Subjects who have clinically significant abnormalities in 12-lead ECG and require treatment or close follow-up (such as Grade II or III atrioventricular block, atrial fibrillation, atrial flutter, pre-excitation syndrome, etc.) at screening (V1); or QT interval corrected by Fridericia formula (QTcF) > 470 ms (male) or QTcF > 480 ms (female) (see APPENDIX 5 for the calculation formula) at screening.
29. Etiological test at screening (V1): positive for hepatitis B surface antigen and hepatitis B viral load (HBV-DNA) above the lower limit of detection of the local laboratory; or positive for anti-hepatitis C antibody and hepatitis C viral load (HCV- RNA) above the lower limit of detection of the local laboratory; or positive for treponema pallidum antibody (TP-Ab); or positive for human immunodeficiency virus antibody (HIV-Ab).
30. Subjects whose laboratory parameters are within any of the following ranges at screening (V1):
    • ALT≥5×upper limit of normal (ULN), AST≥5×ULN;
    • Alkaline phosphatase (ALP) > 2×ULN;
    • Direct bilirubin (DBIL)> 1.5×ULN;
    • TBIL>1.5×ULN;
    • Serum TG ≥4.52 mmol/L (400 mg/dL), or serum LDL-C >5.69 mmol/L (220 mg/dL);
    • Hemoglobin <1×lower limit of normal (LLN);
    • Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (see APPENDIX 5 for calculation formula); or urine protein≥++.
31. Subjects who have donated blood or had massive blood loss (≥400 mL), or received blood transfusion or blood products within 3 months prior to screening.

	32. Subjects who are alcoholism (14 units of alcohol per week: 1 unit = 285 mL beer, or 25 mL liquor, or 100 mL wine) within the 12 months prior to screening and are unable to control alcoholism during the study. 33. Pregnant or lactating female subjects. 34. Partners of the male subjects or the female subjects are planning to become pregnant, or are unwilling to take reliable contraceptive measures (see APPENDIX 6) during the period from the signing of the ICFs to 3 months after the last dose of the investigational drug. 35. Subjects who have participated in clinical studies on other investigational drugs or medical devices, and taken investigational drugs or used medical devices, or used any unapproved treatment methods within 3 months prior to screening. 36. Subjects who have received vaccines (except inactivated vaccines) within 4 weeks prior to screening or planned to receive vaccines (except inactivated vaccines) during the study (from the signing of the ICFs to the end of the safety follow-up visit). 37. Subjects who have the medication compliance <80% or >120% in the single-blind introduction period. 38. Subjects who are considered as not suitable for participating in the study by the investigator due to other conditions.
Drug, Usage and Dosage:	**1) Study Products** **Investigational Drug** Drug name: HTD1801 Capsules Strength: 250 mg/capsule Manufacturer: the drug was provided by Shenzhen HighTide Biopharmaceutical, Ltd., and manufactured by the contract manufacturing organization Shanghai STA Pharmaceutical Product Co., Ltd.. Expiry date: 18 months (it is tentative and will be revised based on the accumulated data on stability studies) Storage conditions: stored in a tight container at room temperature. **Control Drug** Drug name: Placebo Capsules Strength: the capsules correspond to the investigational drug strength, but do not contain any active pharmaceutical ingredient. Manufacturer: the drug was provided by Shenzhen HighTide Biopharmaceutical, Ltd., and manufactured by the contract manufacturing organization Shanghai STA Pharmaceutical Product Co., Ltd.. Expiry date: 18 months (it is tentative and will be revised based on the accumulated data on stability studies) Storage conditions: stored in a tight container at room temperature. **2) Drug for salvage therapy** Drug name: Empagliflozin Strength: 10 mg/tablet Supplier: Shenzhen HighTide Biopharmaceutical, Ltd. Storage condition: stored in a well-closed container (according to the instructions for use) **3) Usage and Dosage** **Single-blind Introduction Period:** The placebo should be taken with meals, 4 capsules, BID. **Double-blind Treatment Phase:** 500 mg BID dose group: 2 HTD1801 capsules (250 mg/capsule) + 2 placebo capsules should be taken with meals (in the standard meal process on the days of V6 and V7: the drug should be taken immediately after the first bite); the dosing frequency should be BID throughout the double-blind treatment phase, except for QD in the evening on the day of V4 (Day 1), and QD in the morning on the day of V7 (Day 84). 1000 mg BID dose group: 4 HTD1801 capsules (250 mg/capsule) should be taken with meals (in the standard meal process on the days of V6 and V7: the drug should be taken immediately after the first bite); the dosing frequency should be BID throughout the double-blind treatment phase, except for QD in the evening on the day of V4 (Day 1),

	and QD in the morning on the day of V7 (Day 84). Placebo group: 4 placebo capsules should be taken with meals (in the standard meal process on the days of V6 and V7: the drug should be taken immediately after the first bite); the dosing frequency should be BID throughout the double-blind treatment phase, except for QD in the evening on the day of V4 (Day 1), and QD in the morning on the day of V7 (Day 84). **Criteria for Initiating Salvage Therapy, and Usage and Dosage of the Drug for Salvage Therapy:** During the double-blind treatment phase, when the investigator is informed that the subject's blood glucose has reached the hyperglycemia threshold for salvage therapy, after excluding the external cause of poor blood glucose control, the investigator should retest the FPG of the subject in the central laboratory within 7 days after being informed of the result (see Section 5.13.3 for details); the hyperglycemia threshold for salvage therapy is as follows: ● First 6 weeks of the treatment phase (including Week 6): FPG≥15.0 mmol/L; ● Week 7-12 of the treatment phase: FPG≥13.3 mmol/L; Based on the central laboratory FPG results, the investigator should determine whether to take the salvage therapy. If the subjects meet the criteria for initiating the salvage therapy, on the basis of treatment with the investigational drug, the investigator will determine the usage and dosage of Empagliflozin according to the conditions of the subjects, and referring to the instructions for use of Empagliflozin and Diagnosis and Treatment Guidelines for Diabetes Mellitus.
Study Procedures	This study includes a screening phase, a single-blind introduction period, a double-blind treatment phase, and a safety follow-up visit phase. **Screening Phase** Subjects who have signed the ICFs will enter a screening phase of up to 2 weeks, and will complete the required screening tests and be assessed for eligibility for inclusion in this study. **Single-blind Introduction Period** Eligible subjects will first enter the 4-week single-blind placebo introduction period. The investigators will instruct the subjects on lifestyle, medication and SMBG during the introduction period. Subjects will be tested for the relevant indicators again (see the study process) prior to randomization (V3). For subjects who are eligible according to the protocol prior to randomization (V3), the HbA1c (7.0%≤HbA1c≤10.5%) tested in the central laboratory prior to randomization (V3) will be used as the baseline value during the treatment phase; the CAP of liver transient elastography measured at each site will be used as the baseline value. **Double-blind Treatment Phase** On the day of the randomization visit, the application of inclusion/exclusion criteria on subjects will be reviewed again based on the test results prior to randomization (V3). Subjects in compliance with the protocol will be randomized into the placebo group, HTD1801 500 mg BID group, and HTD1801 1000 mg BID group at a ratio of 1:1:1 based on the central laboratory HbA1c test results (<8.5% and ≥8.5%) and the CAP (<274 dB/m or ≥274 dB/m) tested by each site prior to randomization (V3), and enter a 12-week double-blind treatment phase. The investigators will instruct the subjects on lifestyle, medication and SMBG during the study. During the study, the subjects will receive the followed-up visit on the specified date once every 4 weeks to evaluate the symptoms and vital signs of the subjects, receive the laboratory tests, and be collected for blood samples for PPK and efficacy endpoints. AEs and concomitant medication, distribution and recovery of investigational drugs, etc. will be recorded. **Safety Follow-up Visit Phase** At the end of the 12-week double-blind treatment phase, all subjects will receive the safety followed-up visit at 4 weeks after the last dose of the investigational drug. For subjects who have received at least one dose of investigational drug and withdraw the study treatment early after randomization, the subjects are recommended to return to the study site for withdrawal follow-up visit within 1 week after confirmed

	withdrawal, and to receive the safety follow-up visit at 4 weeks after the last dose of the investigational drug.
Estimation of Sample Size	**Test Hypothesis Design and Estimation of Sample Size:** Changes from baseline in HbA1c with 12-week treatment were assumed to be -1.1%, -1.4%, and -0.4% for 2 dose groups (500 mg BID and 1000 mg BID) and placebo group, respectively, a pooled standard deviation is 1.1%, and the α level is 0.05 (two-sided). 81 subjects (27 subjects in each group) can provide 90% power to test for the statistical difference between 1000 mg BID dose group and placebo group, and 63% power to test for the statistical difference between 500 mg BID dose group and placebo group. Given the dropout rate of approximately 20%, 99 subjects are planned to be enrolled in the study (33 subjects in each group).
Statistical Analysis	**Statistical Analysis Population** Full analysis set (FAS): according to the basic principle of intention to treat (ITT) analysis, including all subjects who have been randomized in the study and used the investigational drug at least once. Per-protocol set (PPS): including all subjects in the FAS population with good compliance and no serious protocol violations. FAS and the PPS are used in the efficacy analysis. Safety set (SS): including all subjects who have been randomized, used the investigational drug at least once and received at least one subsequent safety assessment. Pharmacokinetics set (PKS): including all subjects who have been randomized, used the investigational drug at least once and had at least one valid data of PK measurement. **Statistical Analytical Methods** Statistical analysis will be calculated by SAS 9.4 or higher version. Subject disposition will be described. Demographic variables and baseline characteristics will be summarized. The efficacy analysis is mainly based on the FAS, and the statistical analysis is based on the PPS. The efficacy analysis is mainly based on the therapy strategy, with the on-treatment strategy as the sensitivity analysis. The primary efficacy endpoint is the change in HbA1c from baseline with 12-week treatment. For the primary efficacy endpoint, the mixed effects model for repeated measures (MMRM) is used for analysis, with the change in HbA1c from baseline as the dependent variable, the treatment group, measurement time point, random stratification factor (CAP≥274 dB/m or CAP < 274 dB/m) as the independent variables, and HbA1c of subjects in baseline as a covariate. Judgments are made based on model-corrected least-squares means differences between groups. Sensitivity analysis is performed using an Analysis of Covariance (ANCOVA) last measurement carried forward (LOCF) model for subjects who withdrew from the study 12 weeks before. For the measurement data in the secondary efficacy endpoints, the same analysis method as the primary efficacy endpoints is used, with the random stratification factors in the model: CAP and HbA1c; for the enumeration data in the secondary efficacy endpoints, invalid filling is applied and the CMH method is used for inter-group comparison, with the random stratification factors in the model: CAP and HbA1c. **Safety Analysis** Based on the SS, the safety analysis is performed based on the therapy strategy. Adverse events (AEs) All AEs are coded by system organ class (SOC) and preferred term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of various AEs, such as AEs, drug-related AEs, serious adverse events (SAEs), and other major medical events, are calculated separately, and a detailed list is provided. The incidence is calculated with the number of subjects in SS in each group as the denominator, and the chi-square test is used (Fisher's exact test is used based on the data) for inter-group comparison if necessary. Hypoglycemia events The number of subjects, percentage and number of cases of hypoglycemia events (Grade 1 hypoglycemia event, Grade 2 hypoglycemia event, Grade 3 hypoglycemia event, etc.) are analyzed.

	Clinical laboratory tests Including hematology, blood biochemistry, urinalysis and coagulation tests, etc. The laboratory test results of each visit and their changes from baseline are described with mean, standard deviation, median, minimum and maximum. The clinical judgment results (normal, abnormal with no clinical significance, abnormal with clinical significance, and not tested) of the laboratory test results at each timepoint before and after treatment are presented in cross tabulation. For subjects with abnormal laboratory test results during the treatment phase, the results of each test and judgment are listed according to the abnormality with clinical significance and the abnormality without clinical significance. Vital signs The results of vital signs in each visit and their changes from baseline are described with mean, standard deviation, median, minimum and maximum. Physical examination The physical examination results of each visit are described, the number of normal and abnormal subjects and percentages are calculated, and abnormal values are listed. 12-lead ECG Refer to the evaluation of laboratory test indicators. **Pharmacokinetic Analysis** The data on blood samples collected in the morning under fasting conditions on V4, and before the first dose of the day on V5, V6, and V7 are summarized to evaluate the trough concentration of multiple-dose HTD1801 in T2DM subjects, and descriptive statistics of the trough concentration are performed. **Population Pharmacokinetic Analysis** See the separate PPK analysis plan for details. **Intestinal Flora Analysis** For details, see the separate analysis plan for intestinal flora.

STUDY PROCESS

		Screening Phase	Single-blind Introduction Period		Double-blind Treatment Phase				Safety Follow-up Visit Phase [3]	Pre-salvage Therapy Visit [4]	Salvage Therapy Evaluation Visit [5]
Visit		**V1[1]**	**V2**	**V3**	**V4[1]**	**V5**	**V6**	**V7/Withdrawal Visit [2]**	**V8**	**Not applicable**	**Not applicable**
Weeks (Days)		**Week -6 to Week -4**	**Week -4**	**Week -1 (Day -7 to Day -5)**	**Day1**	**Week 4 (Day 28)**	**Week 8 (Day 56)**	**Week 12 (Day 84)**	**Week 16 (Day 112)**	**Not applicable**	**Over 4 weeks of salvage therapy**
Visit Window		**Not applicable**	**Not applicable**	**Not applicable**	**Not applicable**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**Not applicable**	**±3 days**
Inclusion and Clinical Evaluation	**Sign the ICFs**	**X**									
	Assign the Subject Screening Number	**X**									
	Demographic Data [6]	**X**									
	Medical History and Surgical History	**X**									
	Medication History	**X**									
	Reviewing Inclusion/Exclusion Criteria	**X**			**X**						
	Randomization				**X**						
	Physical Examination[7]	**X**		**X**		**X**	**X**	**X**			**X**
	Vital Signs [8]	**X**		**X**	**X**	**X**	**X**	**X**			**X**
	Body Height	**X**									

		Screening Phase	Single-blind Introduction Period		Double-blind Treatment Phase				Safety Follow-up Visit Phase [3]	Pre-salvage Therapy Visit [4]	Salvage Therapy Evaluation Visit [5]
Visit		**V1[1]**	**V2**	**V3**	**V4[1]**	**V5**	**V6**	**V7/Withdrawal Visit [2]**	**V8**	**Not applicable**	**Not applicable**
Weeks (Days)		**Week -6 to Week -4**	**Week -4**	**Week -1 (Day -7 to Day -5)**	**Day1**	**Week 4 (Day 28)**	**Week 8 (Day 56)**	**Week 12 (Day 84)**	**Week 16 (Day 112)**	**Not applicable**	**Over 4 weeks of salvage therapy**
Visit Window		**Not applicable**	**Not applicable**	**Not applicable**	**Not applicable**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**Not applicable**	**±3 days**
	Body Weight	**X**		**X**		**X**	**X**	**X**		**X**	
	Etiological test [9]	**X***									
	Blood Biochemistry	**X***		**X***		**X***	**X***	**X***		**X***	**X***
	Hematology	**X***		**X***		**X***	**X***	**X***		**X***	**X***
	Urinalysis	**X***		**X***		**X***	**X***	**X***		**X***	**X***
	Blood Pregnancy Test	**X***		**X***				**X***			
	Urine Pregnancy Test [10]					**X***	**X***				
	Coagulation Tests	**X***		**X***				**X***			
	Thyroid Function Tests [11]	**X***									
Visit Request	**Fasting [13]**	**X**		**X**	**X**	**X**	**X**	**X**		**X**	**X**
Evaluation Endpoint [12]	**HbA1c [13]**	**X***		**X****			**X****	**X****		**X****	
	Fasting Blood Glucose [13]	**X***		**X****	**X****	**X****	**X****	**X****		**X****	**X****
	Postprandial				**X****		**X****	**X****			

		Screening Phase	Single-blind Introduction Period		Double-blind Treatment Phase				Safety Follow-up Visit Phase [3]	Pre-salvage Therapy Visit [4]	Salvage Therapy Evaluation Visit [5]
Visit		**V1[1]**	**V2**	**V3**	**V4[1]**	**V5**	**V6**	**V7/Withdrawal Visit [2]**	**V8**	**Not applicable**	**Not applicable**
Weeks (Days)		**Week -6 to Week -4**	**Week -4**	**Week -1 (Day -7 to Day -5)**	**Day1**	**Week 4 (Day 28)**	**Week 8 (Day 56)**	**Week 12 (Day 84)**	**Week 16 (Day 112)**	**Not applicable**	**Over 4 weeks of salvage therapy**
Visit Window		**Not applicable**	**Not applicable**	**Not applicable**	**Not applicable**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**Not applicable**	**±3 days**
	Blood Glucose [14]										
	Fasting Insulin [13]				**X****	**X****	**X****	**X****		**X****	
	Postprandial Insulin [14]				**X****		**X****	**X****			
	Fasting C-peptide [13]				**X****	**X****	**X****	**X****		**X****	
	Postprandial C-peptide [14]				**X****		**X****	**X****			
	C-reactive Protein [13]				**X****			**X****		**X****	
	Liver Function and Blood Lipid Test [13,15]				**X****	**X****	**X****	**X****		**X****	
	Feces Collection (if any)[16]				**X****		**X****	**X****		**X****	
	Intestinal Flora Metabolomics Serum Samples				**X****		**X****	**X****		**X****	
	PPK Blood Sample Collection [17]				**X****	**X****	**X****	**X****		**X****	

		Screening Phase	Single-blind Introduction Period		Double-blind Treatment Phase				Safety Follow-up Visit Phase [3]	Pre-salvage Therapy Visit [4]	Salvage Therapy Evaluation Visit [5]
Visit		**V1[1]**	**V2**	**V3**	**V4[1]**	**V5**	**V6**	**V7/Withdrawal Visit [2]**	**V8**	**Not applicable**	**Not applicable**
Weeks (Days)		**Week -6 to Week -4**	**Week -4**	**Week -1 (Day -7 to Day -5)**	**Day1**	**Week 4 (Day 28)**	**Week 8 (Day 56)**	**Week 12 (Day 84)**	**Week 16 (Day 112)**	**Not applicable**	**Over 4 weeks of salvage therapy**
Visit Window		**Not applicable**	**Not applicable**	**Not applicable**	**Not applicable**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**Not applicable**	**±3 days**
Radiography and Auxiliary Examinations	**12-lead ECG [18]**	**X***		**X***	**X***	**X***	**X***	**X***		**X***	**X***
	Liver Transient Elastography (including LSM and CAP)	**X***		**X***				**X***		**X***	
	Abdominal Color Doppler Ultrasound (kidneys, liver, gallbladder, pancreas, spleen)			**X***							
Treatment	**Guidance on Lifestyle**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**
	Self-monitoring of Blood Glucose [19]		**X**								
	Guidance on Investigational Drug		**X**	**X**	**X**	**X**	**X**				
	Distribution of Investigational Drug		**X**		**X**	**X**	**X**				

		Screening Phase	Single-blind Introduction Period		Double-blind Treatment Phase				Safety Follow-up Visit Phase [3]	Pre-salvage Therapy Visit [4]	Salvage Therapy Evaluation Visit [5]
Visit		**V1[1]**	**V2**	**V3**	**V4[1]**	**V5**	**V6**	**V7/Withdrawal Visit [2]**	**V8**	**Not applicable**	**Not applicable**
Weeks (Days)		**Week -6 to Week -4**	**Week -4**	**Week -1 (Day -7 to Day -5)**	**Day1**	**Week 4 (Day 28)**	**Week 8 (Day 56)**	**Week 12 (Day 84)**	**Week 16 (Day 112)**	**Not applicable**	**Over 4 weeks of salvage therapy**
Visit Window		**Not applicable**	**Not applicable**	**Not applicable**	**Not applicable**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**Not applicable**	**±3 days**
	Dosing Regimen [20]		**X**		**X**						
	Recovery of Investigational Drug			**X**	**X**	**X**	**X**	**X**			
	Distribution of Salvage Therapy Drug [21]									**X**	**X[21]**
	Distribution of Subject Diary		**X**		**X**	**X**	**X**				
	Recovery of Subject Diary			**X**	**X**	**X**	**X**	**X**			
	Compliance Assessment			**X**	**X**	**X**	**X**	**X**			
	Recording of Concomitant Medications or Non-drug Therapy	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
	Recording of AEs	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Note:

1. If V1 and V2 are on the same day, the two visits can be pooled into one visit. The laboratory test, 12-lead ECG, and fasting plasma glucose (FPG) test results within 1 week prior to screening (including before signing the ICFs) in this study site are accepted (if plasma glucose cannot be tested, serum glucose results are acceptable); HbA1c test results within 4 weeks prior to screening in this study site are accepted. The test indicators on the day of randomization (V4) are not used as the basis for the inclusion/exclusion review.
2. Withdrawal visit: only for subjects who have received investigational drug and withdraw the study treatment after randomization. For subjects who withdraw their ICFs, the subjects are recommended to return to the study site for a withdrawal visit within 1 week after confirmed withdrawal. The withdrawal visit procedure is the same as that of V7. If the subject withdraws early during the safety follow-up visit, the visit procedure should be the same as that of the safety follow-up visit (V8).
3. Safety follow-up visit (V8) is conducted by telephone visit to inquire about the occurrence of AEs and concomitant medication. If the subject should be re-tested according to the investigator's judgment on the laboratory results of the subject at Week 12, then the subject should be arranged to come to the study site for follow-up visit. For subjects who failed in the randomization and who did not receive the investigational drug after randomization, no 4-week post-dose safety follow-up visit is required. During the safety follow-up visit, the investigator can give the subjects other anti-diabetic drug treatment (without berberine and ursodeoxycholic acid) according to the subject's condition and diagnosis and treatment guidelines for diabetes mellitus.
4. Pre-salvage therapy visit: investigators should retest the fasting plasma glucose of the subject in the central laboratory within 7 days after being informed that the subject's test result has reached the hyperglycemia threshold for salvage therapy. Subjects whose central laboratory re-test results meet the hyperglycemia threshold for salvage therapy will receive the pre-salvage therapy visit before the salvage therapy. If the time point between the pre-salvage therapy visit and the follow-up routine visit (V5 or V6) in the double-blind treatment phase is $\leqslant$7 days, the next treatment visit (V5 or V6) is not required. If the subject has contraindications to salvage therapy, the pre-salvage therapy visit is not required, and the subject should withdraw from the study early and receive the withdrawal visit.
5. Salvage therapy evaluation visit: if the subject has received salvage therapy for 4 weeks during the 12-week double-blind treatment phase, a salvage therapy evaluation visit is required to evaluate the effect of salvage therapy by FPG; if the salvage therapy evaluation visit time (including the visit window) coincides with the routine visit time (including the visit window) during the double-blind treatment phase, they will be pooled into one visit, and the content of the visit should meet the requirements of both visits; the effect of salvage therapy will be evaluated according to FPG . If the subject's FPG does not reach the corresponding hyperglycemia threshold set in the protocol, it is defined as success in salvage therapy, and the subject will continue to use salvage therapy drugs in addition to the investigational drug according to the protocol. If the subject's FPG reaches the corresponding hyperglycemia threshold set in the protocol, it is defined as failure in salvage therapy, and the subject will withdraw from the study and receive a withdrawal visit. If the subject is receiving salvage therapy at the end of the 12-week double-blind treatment phase, but the salvage therapy duration was less than 4 weeks, the salvage therapy evaluation visit is not required, and the V7 visit is carried out according to the normal procedure.
6. Demographic data: information such as gender, age, ethnicity and/or date of birth, etc.
7. Physical examinations: skin, mucous membranes, lymph nodes, head, neck, chest, abdomen, spine/limbs.

8. Vital signs: pulse, temperature, sitting blood pressure (systolic and diastolic) measurement. Subjects should be measured at rest. It is recommended that blood pressure be measured on the same arm for each subject at each visit throughout the study.
9. Etiological test: including hepatitis B virus surface antigen (HBsAg), hepatitis B virus (HBV-DNA) test (if necessary), hepatitis C virus antibody (HCV-Ab), hepatitis C virus (HCV-RNA) test (if necessary), treponema pallidum antibody (TP-Ab), human immunodeficiency virus antibody (HIV-Ab).
10. Pregnancy test: for female subjects of childbearing age only (see APPENDIX 6). The blood pregnancy test is required at V1, V3, and V7 in the local laboratory. During the study V5 and V6, a urine pregnancy test should be performed in local laboratories, and if the urine pregnancy test is positive, a blood pregnancy test should be performed immediately to exclude or verify the pregnancy. If the blood pregnancy test at V1 is positive, the subject will not be able to participate in the study. Female subjects should withdraw from the study immediately once the blood pregnancy test is positive.
11. Thyroid function tests: free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH).
12. Evaluation endpoints: for the sample collection time window, see APPENDIX 8.
13. Except for the blood samples collected after meals, other blood samples should be collected under the fasting condition (V1, V3, V4-7, withdrawal visit, pre-salvage therapy visit, and salvage therapy evaluation visit). It is recommended to collect the fasting blood samples at 7:00 ~ 10:00 a.m.
14. After meals: standard meals are given. For detailed procedures, please refer to APPENDIX 9. For the time window, please refer to the APPENDIX 8.
15. Liver function and blood lipid test: for LDL-C, HDL-C, TG, TC, AST, ALT, GGT, TBIL, the time windows are shown in APPENDIX 8.
16. Feces collection (if any): feces samples of subjects should be collected from the day before the visit to the day of the visit according to the subject's own conditions if possible. Refer to the *Laboratory Operation Manual* for the relevant procedures of feces collection. A lifestyle background survey can be conducted at the same time as the baseline feces collection to better guide the subject's lifestyle.
17. PPK blood sample collection: V4 blood samples should be collected under the fasting condition in the forenoon, V5-V7 blood samples should be collected before breakfast on the same day (before the first administration) (time window: within 1 hour before dosing).
18. 12-lead ECG: subjects should be checked in the supine position after rest, and the heart rate, PR interval, QT interval, RR interval, QTcF (see APPENDIX 5 for calculation formula) and QRS complex duration should be recorded.
19. Subjects' self-monitoring of blood glucose: the subjects should be monitored for the fasting or postprandial fingertip blood glucose at home as required, and measured as required during the introduction period. The recommended test frequency during the double-blind treatment phase is 1-2 times a week. Additional blood glucose measurement is required when symptoms of hypoglycemia or hyperglycemia are suspected and recorded in the subject diary. At each visit, the investigator needs to carefully review the subject diary, and provide suggestions for the subject's following blood glucose monitoring according to the records in the subject diary. For detailed procedures, please refer to APPENDIX 10.
20. Dosing regimen: during the introduction period, all subjects are given the placebo, and are administered with the corresponding investigational drug according to the grouping of subjects after randomization. Salvage therapy is to use the salvage drug in addition to the investigational drug.
21. Distribution of the salvage therapy drug: it is only applicable when the salvage therapy is successful, and will be distributed together with the investigational drug in the follow-up routine visits during the double-blind treatment phase.

*The local laboratory is responsible for testing and feedback of measurements.
**The central laboratory is responsible for unified testing.

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LIST OF ABBREVIATIONS

Abbreviation	Full Name in English
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the curve from pre-dose to the time of the last observation
BBR	Berberine
BBR·Cl	Berberine hydrochloride
BID	Twice a day
BMI	Body mass index
CAP	Controlled attenuation parameter
CDE	Center for drug evaluation, national medical products administration
C_{max}	Maximum plasma concentration
CRO	Contract research organization
CTCAE	Common terminology criteria for adverse events
CYP450	Cytochrome P450
DBIL	Direct bilirubin
DPP-4	Dipeptidyl peptidase IV
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and drug administration
FPG	Fasting plasma glucose
FXR	Farnesoid X receptor
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good clinical practice
GGT	Gamma-Glutamyl Transferase
GLP-1	Glucagon-like peptide-1
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B virus surface antigen
HCV-Ab	Hepatitis C virus antibody
HDL-C	High-density lipoprotein cholesterol
HED	Human equivalent dose
HIV-Ab	Human immunodeficiency virus antibody
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
IR	Insulin resistance
ITT	Intention-to-treat analysis
LDL-C	Low-density lipoprotein cholesterol
LLN	Lower limit of normal
LOCF	Last observation carried forward

Abbreviation	Full Name in English
LSM	Liver stiffness measurement
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measures
MTD	Maximum tolerated dose
NASH	Nonalcoholic steatohepatitis
NOAEL	No observed adverse effect level
NYHA	New york heart association
PKS	Pharmacokinetic set
PPK	Population pharmacokinetics
PPS	Per protocol set
PSC	Primary sclerosing cholangitis
PT	Preferred terms
QA	Quality assurance
QTcF	Corrected QT interval by Fredericia's formula
SAE	Serious adverse event
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
SOC	System organ class
SS	Safety set
SOP	Standard operation procedure
SUSAR	Suspected unexpected serious adverse reaction
SMBG	Self-monitoring of blood glucose
T2DM	Type 2 diabetes mellitus
TBIL	Total bilirubin
TC	Total cholesterol
TG	Triglyceride
TGR5	Takeda G protein-coupled receptor 5
TP-Ab	Treponema pallidum antibody
TSH	Thyroid stimulating hormone
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
UGT	UDP-glucuronosyltransferase
WHO	World health organization
WHO DD	World health organization drug dictionary

GLOSSARY

Investigational Drug	HTD1801
Control Drug	Placebo
Study Products	Invstigational drug and control drug
Drug for Salvage Therapy	Empagliflozin

1. STUDY BACKGROUND

1.1 Disease Introduction

In the past 40 years, with the aging of our country's population and changes in lifestyles, more and more people are diagnosed with diabetes. According to the World Health Organization (WHO) diabetes etiology classification system (1999), diabetes is divided into 4 categories based on etiological evidence, namely Type 1 diabetes mellitus, Type 2 diabetes mellitus (T2DM), special diabetes and gestational diabetes. T2DM is predominant in Chinese patients, accounting for more than 90.0% of the overall diabetic population[1,2]. The national epidemiological survey showed that in 2013, the prevalence of T2DM in Chinese adults was 10.4%. According to the information disclosed in the newly released "Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition)", as of 2017, the prevalence of diabetes in China has reached 11.2%. There are currently more than 150 million diabetic patients in China, ranking first worldwide[3,4].

Type 2 diabetes mellitus (T2DM) is a progressive disease. Its specific etiology and pathogenesis are not yet clear, but current research showed that in the natural course of T2DM, its significant pathophysiological feature is the decline in insulin's ability to regulate glucose metabolism, that is, insulin resistance (IR) accompanied by a decrease (or a relative decrease) in insulin secretion caused by deficient pancreatic β-cell function. IR is more obvious in obese T2DM patients. In recent years, studies have shown that the prevalence of diabetes in obese and overweight people has increased significantly, and the prevalence of diabetes in obese people has increased by 2 folds. In 2013, the prevalence of diabetes in people with body mass index (BMI) <25 kg/m^2 was 7.8%, the prevalence in people with 25 kg/m^2≤BMI<30 kg/m^2 was 15.4%, and the prevalence in people with BMI≥30 kg/m^2 reached 21.2%[3].

Effective blood glucose control is the primary goal of therapeutic intervention for patients with T2DM. The patient's long-term hyperglycemia state can cause systemic macrovascular and microvascular diseases, affecting heart, kidney, brain and other organs, leading to complications such as diabetic nephropathy, diabetic retinopathy, stroke, cardiovascular disease, and diabetic neuropathy. Diabetic nephropathy is the leading cause of end-stage renal disease; diabetic retinopathy is the leading cause of blindness in adults; diabetic neuropathy is the leading cause of nontraumatic distal amputation. The cardiovascular mortality and stroke incidence in diabetic patients are both 2-4 times higher than that of normal people. Patients with nonalcoholic fatty liver disease complicated with T2DM usually suffer from severe liver injury[4]. Complications of diabetes not only endanger the health of patients, but also bring a heavy economic burden to the family and society, occupying a lot of medical resources. Studies have shown that 81% of diabetes-related medical expenses in China are used to treat various complications. The annual direct medical expenses of T2DM patients with complicated microvascular or macrovascular disease or both are 3.18 times, 4.13 times and 10.35 times that of T2DM patients without complicated disease, respectively. Therefore, intervention is crucial for diabetic patients, so as to achieve early diagnosis, early treatment and early control, and to delay the progression of the disease[5].

The currently available oral medications for T2DM are mainly used for correcting IR and the impaired insulin secretion. According to mechanisms of action, oral hypoglycemic drugs can be divided into drugs whose main function is to promote insulin secretion, including sulfonylureas, non-sulfonylureas, biguanides, glucosidase inhibitors and thiazolidinediones, etc. and drugs that lower blood glucose through other mechanisms, such as dipeptidyl peptidase IV (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose co-transporter-2 inhibitor (SGLT-2i), insulin analogs, etc. In addition, metabolic surgery can also be considered for obese T2DM patients.

Although there are many kinds of hypoglycemic drugs on the market, as a country with a high incidence of T2DM and a large number of patients, China's overall diabetes prevention and control efficiency is still insufficient, with the blood glucose control rate merely achieving 33.0%[6]. For T2DM patients complicated with underlying diseases such as hypertension, hyperlipidemia and liver disease in China, there is still a lack of safe and effective treatment options. Therefore, it is of great significance to develop innovative drugs with comprehensive therapeutic effects for T2DM.

HTD1801 is developed by Shenzhen HighTide Biopharmaceutical, Ltd. It is a new ionic salt compound formed by BBR and ursodeoxycholic acid (UDCA) in a ratio of 1:1. Existing clinical studies have shown that it has a down-regulating effect on glycosylated hemoglobin (HbA1c) with good safety. This product is an oral capsule intended for the treatment of patients with T2DM. HTD1801 is an innovative drug that has not been marketed at home or abroad. According to the "Announcement of NMPA on Issuing the Registration Classification and Submission Dossier Requirements of Chemical Drugs (No. 44 of 2020)", this product is applied under Registration Classification: Class 1 Chemicals.

1.2 Drug Introduction

1.2.1 Drug name and physicochemical characterization

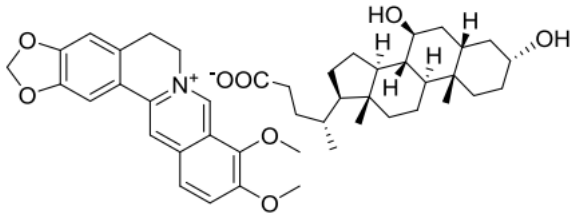
Generic name of drug product: HTD1801 Capsules

Active ingredients: HTD1801

Chinese chemical name: 5,6-二氢-9,10-二甲氧苯并[g]-1,3-苯并二氧戊环[5,6-a]喹嗪,3α,7β-二羟基-5β-胆甾烷-24-酸盐

English chemical name: 9,10-dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ium(R)-4-((3R,5S,7S,8R,9S,10S,13R,14S,17R)-3,7-dihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate

Structural formula:



Molecular formula: $C_{44}H_{57}NO_8$

Molecular weight: 727.94 g/mol

1.2.2 Mechanism of action

HTD1801 is an ionic salt formed by BBR and UDCA. Based on the additive and synergistic effects of the two active moieties, the known mechanisms of BBR and UDCA alone can be referred to the investigation of mechanism of HTD1801. We made the following overview based on the relevant literature on the pharmacological effects of the two moieties, aiming to provide a scientific basis for the use of HTD1801 in the treatment of T2DM.

1.2.2.1 Berberine (BBR)

At present, a large number of clinical study data have validated BBR's effect in regulating glucose metabolism. Fourteen randomized clinical trials, involving 1068 participants, were summarized in a systematical review with meta-analysis. The results showed good safety of BBR in patients with T2DM. In terms of therapeutic potential, compared with traditional hypoglycemic drugs (Metformin, Glipizide, Rosiglitazone, etc.), BBR demonstrated an equivalent hypoglycemic effect as well as slightly superior antilipemic effect. Compared with monotherapy of traditional hypoglycemic drugs, concomitant use of traditional drugs and BBR showed a better hypoglycemic effect[7].

According to previous study results, BBR mainly improves blood glucose metabolism by increasing glucokinase activity, increasing insulin secretion, inhibiting liver gluconeogenesis and adipogenesis, etc.[8] In addition, Professor Jia Weiping et al. [9,10] pointed out in their research that for typical T2DM disease accompanied with obvious IR, BBR was able to enhance insulin sensitivity and lower blood insulin level; while in patients at late stage of T2DM characterized by poor β-cell function, BBR may improve insulin secretion by repairing destructed islets, which may be related to its antioxidant and anti-lipid peroxidation properties. In summary, BBR has a multi-organ, multi-target/pathway hypoglycemic effect[8,9,11], which is expected to bring therapeutic benefits to patients at different stages of T2DM.

In addition, it is worth noting that previous clinical studies have shown that BBR also effectively lowered FPG level in patients with T2DM or glucose metabolism disorders complicated with chronic hepatitis B or hepatitis C. In these patients, liver function was also improved manifested as reduction of liver enzymes[12]. At present, the main medications for T2DM treatment, biguanides and sulfonylureas, are banned for patients with hypohepatia. BBR can not only produce similar hypoglycemic effect as the traditional hypoglycemic drugs, but also protect the liver, providing treatment options for T2DM patients with liver injury. Hypoglycemic mechanisms of BBR are as follows (see the Investigator's Brochure for details):

(1) BBR inhibits gluconeogenesis and increases insulin sensitivity;

(2) BBR promotes glycolysis;

(3) BBR inhibits the intestinal absorption of carbohydrates in the diet;

(4) BBR reduces fat production and cholesterol production;

(5) BBR exhibits anti-inflammatory and anti-oxidative stress effects;

(6) BBR exhibits antibacterial and intestinal protective effects.

1.2.2.2 Ursodeoxycholic acid (UDCA)

At present, the metabolic regulation effect of bile acids has attracted more and more attention from scholars. It is generally believed that bile acids regulate metabolism through two pathways: activation of the intestinal bile acid receptor, takeda G protein-coupled receptor 5 (TGR5), and inhibition of the intestinal farnesoid X receptor (FXR)[13,14].

(1) UDCA improves IR

In the rat model of fructose-induced metabolic syndrome, treatment with UDCA successfully relieved a series of metabolism problems induced by fructose, including increase in body weight, hyperglycemia, hyperinsulinemia, high triglycerides, and high cholesterol, and ameliorated IR of the modeled animals[15].

(2) UDCA promotes insulin secretion

According to literature report, a study in healthy subjects found that compared with UDCA without meals, UDCA with meals resulted in significantly higher GLP-1 secretion and a tendency of higher insulin secretion[16]. In addition, in a clinical study in patients with T2DM complicated with chronic liver disease, UDCA (900 mg/day, 12 weeks) treatment resulted in a greater reduction in HbA1c levels, and an increased early phase GLP-1 secretion[13].

(3) UDCA protects liver

The liver is the core organ for blood sugar metabolism. Therefore, the liver protection function is worthy of attention. As an effective liver protective drug, UDCA has shown clear anti-inflammatory and anti-oxidative stress effects to protect hepatocytes[17-19].

(4) UDCA regulates intestinal bile acid secretion

It has been reported that glycoursodeoxycholic acid (UDCA's main conjugate in the human body) has an inhibition on intestinal FXR[20]. Furthermore, some studies believe that UDCA does not directly affect intestinal FXR and TGR5, but exerts an indirect effect by regulating bile acids: UDCA promotes the secretion of primary bile acids from the liver into the intestine, increasing the primary bile acid conjugate level in the intestine, thereby enhancing the inhibition on intestinal FXR; at the same time, the level of secondary bile acid produced in the intestine rises correspondingly, which in turn strengthens the activity of TGR5[13].

1.2.2.3 HTD1801

HTD1801 is an ionic salt formed by BBR and UDCA. As an approved drug, BBR has a history of human use for many years in China. UDCA is the basic drug for cholestatic diseases. Based on the published study results, we understood that BBR and UDCA exert their therapeutic effects on T2DM through different mechanisms of action, including but not limited to: inhibiting gluconeogenesis, increasing insulin sensitivity, and improving IR; promoting glycolysis; inhibiting intestinal absorption of dietary carbohydrates; taking protective effect of liver and intestines, regulating intestinal bile acid secretion, and protecting liver cells; reducing fat and cholesterol production; exerting anti-inflammatory and anti-oxidative stress effects.

1.2.3 Non-clinical studies

1.2.3.1 Pharmacodynamic studies

Since the Sponsor has observed the significant hypoglycemic effect of HTD1801 in T2DM patients in clinical studies, and summarized the related studies of BBR and UDCA in the treatment of T2DM to further support the therapeutic potential of HTD1801 for T2DM, no separate non-clinical pharmacodynamic studies were carried out for T2DM.

1.2.3.2 Pharmacokinetic studies

After a single dose of HTD1801 in SD rats, the the systemic exposure of BBR and UDCA from time 0 to the last accurately measurable concentration time t (AUC_{0-t}) and the maximum plasma concentration (C_{max}) were increased with dose; the exposure of female rats to BBR at the same dose was about 0.684-0.974 times that of males, and the exposure of female rats to UDCA at the same dose was about 0.571-1.51 times that of males. The $t_{1/2}$ of most animals could not be measured due to too low plasma concentration and enterohepatic circulation in UDCA. After a single oral dose in beagle dogs, the systemic exposure AUC_{0-t} and C_{max} were increased with dose (the exposure gradually reached the plateau at the high dose of 200 mg/kg), and there was no significant gender difference in the exposure of dogs at the same dose. The $t_{1/2}$ of most animals could not be measured due to too low plasma concentration and enterohepatic circulation in UDCA. SD rats (500 mg/kg) were administered once a day for 182 consecutive days; Beagle dogs (200 mg/kg) were administered once a day for 272 consecutive days, and no significant drug

accumulation was observed.

After single dose of HTD1801, Berberine hydrochloride (BBR·Cl), UDCA and physical mixture at the same molar dose in SD rats, compared with the BBR·Cl and UDCA treatment groups, the plasma BBR exposure of the test animals was significantly increased after a single dose of HTD1801, which was 6.6 times that of the BBR·Cl monotherapy group; the exposure of UDCA was comparable to the other two groups. The results of this study suggested that HTD1801 may improve the bioavailability of BBR by forming a new salt form/crystal form.

After a single oral dose of 200 mg/kg HTD1801 in SD rats, the absorption and distribution were rapid, and BBR was mainly distributed in the contents of the gastrointestinal tract, gastrointestinal tract wall, liver, kidney, bile, and blood, and was widely distributed in tissues and quickly eliminated; there was no significant accumulation and residue in each tissue. UDCA was mainly distributed in the contents of the gastrointestinal tract, gastrointestinal wall, esophagus, liver, bile, aorta, blood, kidney, pancreas, and spleen, and was widely distributed in tissues and quickly eliminated; there was no significant accumulation and residue in each tissue.

The inhibition method with the specific chemical inhibitor and the enzyme metabolism method with recombinant human cytochrome P450 (CYP450) showed the consistent results, indicating that CYP3A is the main metabolic enzyme of HTD1801.

The excretion test in SD rats at 0-168 hours showed that feces were the main excretion route.

The results of drug interaction studies showed that HTD1801 had no or weak inhibition on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 (50% inhibitory concentration [IC_{50}] was much higher than clinical C_{max}); the CYP2D6 inhibition IC_{50} was 4.31 μg/mL, the inhibition of HTD1801 on CYD2D6 was weaker than that of BBR·Cl alone, and the IC_{50} was also much higher than the clinical C_{max}. Since no additional inhibition of HTD1801 on CYP450 enzymes was observed compared with BBR·Cl alone, the effect of HTD1801 on CYP450 enzymes is most likely caused by the known inhibitory activity of BBR on CYP450 enzymes, and the clinical exposure of C_{max} was much lower than the inhibitory concentrations above, it is reasonable to predict that the risk of drug interactions due to cytochrome enzyme inhibition is low.

Human liver microsomal chemical inhibitors and recombinant human glucuronyltransferases (UGTs) were used to identify the phenotypes of enzymes involved in HTD1801 glucuronide-binding metabolism, and the results showed that common UGTs related to drug metabolism cannot mediate the glucuronidation of BBR. UGT1A3, UGT1A4, UGT1A8, UGT1A9, UGT2B7, UGT2B15 and UGT2B17 can catalyze the production of glucuronidation metabolites of UDCA to varying degrees; UGT1A1, UGT1A6, UGT1A7, UGT1A10 and UGT2B4 cannot catalyze the production of UDCA glucuronidation metabolites.

The results of the *in vitro* recombinant UGTs model study showed that HTD1801 had generally no inhibition on UGT1A1, UGT1A3, UGT2B7 and UGT2B15. It had certain inhibition on UGT1A9 and UGT2B17.

The results of the interaction test between HTD1801 and bile salt efflux pump (BSEP) suggested that HTD1801 is not a substrate of BSEP; HTD1801 inhibits BSEP to a certain extent. According to the existing test results, the half-maximal inhibition concentration of HTD1801 on BSEP is greater than 100 μM.

The current clinical human steady-state plasma exposure level is far below the concentration of HTD1801 that has a potential inhibition on related CYP enzymes, UGTs, and BSEP obtained *in vitro* studies. Therefore, it is judged that the risk of *in vivo* drug interaction with HTD1801 is low.

1.2.3.3 Repeated-dose toxicology

The results of the 91-day repeated oral dose study of HTD1801 in Beagle dogs showed that the daily maximum tolerated dose (MTD) of HTD1801 was 200 mg/kg and the human equivalent dose (HED) was 108 mg/kg. The No-Observed-Adverse-Effect Level (NOAEL) was determined to be 60 mg/kg, and the HED was 32.4 mg/kg. The results suggest that the gastrointestinal tract and the gallbladder are the target organs. The change in bile retention in the gallbladder was considered to be caused by the pharmacological effect of UDCA in promoting bile acid secretion.

The results of the 39-week repeated oral dose study of HTD1801 in Beagle dogs showed that the MTD was up to 200 mg/kg and the HED was up to 108 mg/kg. The NOAEL of HTD1801 was determined as 75 mg/kg, and the HED was 40.5 mg/kg. Its toxic target organ was determined to be the large intestine (cecum, colon, and rectum).

The results of the 26-week repeated oral gavage study of HTD1801 in SD rats showed that the MTD was up to 500 mg/kg and the HED was 80 mg/kg. The NOAEL was 50 mg/kg for males and 500 mg/kg for females, and the HED was 27 mg/kg and 80 mg/kg, respectively. In this study, although reversible, coagulative necrosis in males at doses $\geqslant$150 mg/kg was considered as an adverse reaction. In order to assess the possible risk of hepatotoxicity caused by HTD1801, the Sponsor commissioned an independent Study Institution BioIVT Labs to explore the toxic effects of BBR, UDCA and the combined administration of both in rats and human hepatocytes through *in vitro* studies. No cytotoxicity of BBR in rats or human hepatocytes was observed at all test doses; rat hepatocytes were more sensitive than human hepatocytes to the cytotoxicity of high-dose UDCA; the toxicity of UDCA used in combination with BBR was significantly lower than that of UDCA alone, which proves that BBR has a certain hepatoprotective effect. In addition, although rats are commonly used species in toxicology studies, and their metabolism of BBR is similar to that of humans, there are multiple studies confirming that the use of rodent models such as rats and mice to evaluate the toxicity of UDCA in humans is of limited applicability. A recent study co-published by Ashby, Navarro and the U.S. food and drug administration (FDA) concluded that due to the significant differences between rodents and humans in bile acid structure, metabolism and elimination, there may be some limitations on the safety of bile acid-containing drugs [21].

1.2.3.4 Carcinogenic toxicity profile

In Non-Tg.rasH2 mice administered once a day for 4 consecutive weeks, the MTD was 1000 mg/kg, and the HED was 80 mg/kg. The results showed that at doses of 1000 and 2000 mg/kg, male animals had increased red blood cells, hemoglobin and hematocrit, and decreased reticulocytes and white blood cells that may be related to the test article; at 2000 mg/kg, male animals had decreased Monocytes, large unstained cells, total protein, globulin, and albumin; one male animal had increased ALT, AST, creatine kinase, and lactate dehydrogenase.

1.2.3.5 Reproductive toxicity profile

The results of the Phase I reproductive toxicity study in SD rats showed that the NOAEL dose for male and female fertility was 2000 mg/kg, and the HED was 320 mg/kg. In female animals in the 2000 mg/kg dose group, a trend towards decreased live fetuses and increased resorbed fetuses was observed; therefore, the NOAEL of HTD1801 for early embryonic development was 1000 mg/kg and the HED was 160 mg/kg.

The results of the reproductive toxicity study with two-study design in SD rats showed that the maternal NOAEL dose was 1000 mg/kg. At the 2000 mg/kg dose, the live fetus body weight and the number of sacrococcygeal bones were slightly reduced; therefore, the NOAEL dose for embryo-fetal development was 1000 mg/kg and the HED was 160 mg/kg. No fetal teratogenic toxicity was observed at 500, 1000, and 2000 mg/kg doses.

1.2.4 Clinical study

Two Phase I clinical studies and one Phase II clinical study of HTD1801 have been completed overseas, and one Phase I and one Phase II clinical studies are in progress (all subjects have been enrolled and dosed). See the table below for details (see the *Investigator's Brochure* for specific study results).

Table 1 Summary of Completed and Ongoing Clinical Studies

Item Number	Study Phase	Study Objectives	Design and Control	Dosage and Route of Administration	HTD1801/Placebo (Number of Subjects)	Subjects Population	Duration of Treatment
HTD1801.PCT002	I	Safety/tolerability and PK of single, ascending doses of HTD1801	Randomized, double-blind, placebo-controlled	500-4000 mg/day (oral)	24/8	Healthy subjects	Single dose
HTD1801.PCT101	I	To evaluate the safety and tolerability and PK of single-dose of investigational drug in Chinese adult healthy subjects	Randomized, double-blind, placebo-controlled	500-2000 mg/day (oral)	18/6	Healthy subjects	Single dose
HTD1801.PCT004	Ib/IIa	Safety/tolerability and PK of multiple ascending doses of HTD1801	Randomized, double-blind, placebo-controlled	500-2000 mg/day (oral)	38/12	Hypercholesterolemia	4 weeks
HTD1801.PCT003	II	Efficacy and safety	Randomized, double-blind, placebo-controlled	1000-2000 mg/day (oral)	53/35*	PSC	Not more than 18 weeks
HTD1801.PCT012	II	Efficacy and safety	Randomized, double-blind, placebo-controlled	1000-2000 mg/day (oral)	67/33	NASH complicated with T2DM	18 weeks

PSC = Primary sclerosing cholangitis; NASH = Nonalcoholic steatohepatitis; T2DM = Type 2 diabetes mellitus; PK = Pharmacokinetics

*In accordance with the clinical study protocol, 55 subjects had been enrolled in the completed PSC clinical study, of which 53 subjects had taken HTD1801, 35 subjects had taken placebo and 2 subjects had only taken placebo during the whole clinical study period.

The Sponsor has completed 4 clinical studies by now, including 2 Phase I clinical studies and 2 Phase II clinical studies:

A first-in-human, randomized, double-blind, single-center clinical study of HTD1801 (HTD1801.PTC002) was completed in Australia. 32 healthy subjects were included in this study, of which 24 subjects in dose groups 1, 2, 3 and 4 were administered with single dose of HTD1801 at doses of 500 mg, 1000 mg, 2000 mg or 4000 mg, respectively.

A multicenter, randomized, double-blind, placebo-controlled, multiple-dose escalation study (HTD1801.PCT004) to evaluate the safety and tolerability of HTD1801 in adult

hypercholesterolemic subjects was completed in Australia. A total of 50 subjects were randomized, and 47 subjects completed the study, of which 35 subjects in dose groups 1, 2, 3 and 4 were administered with HTD1801 at 500 mg/day, 1000 mg/day, or 2000 mg/day, respectively, BID (except QD on Days 1 and 28), for 28 consecutive days.

A randomized, double-blind, placebo-controlled Phase II clinical study to evaluate the efficacy and safety of HTD1801 in adult T2DM subjects with nonalcoholic steatohepatitis (NASH) was completed in the United States (HTD1801.PCT012). A total of 100 subjects were treated in the study, including 34 subjects in the HTD1801 1000 mg BID group, 33 subjects in the HTD1801 500 mg BID group, and 33 subjects in the placebo group.

A randomized, double-blind, placebo-controlled Phase II clinical study to evaluate the efficacy and safety of HTD1801 in adult subjects with a rare disease, i.e., primary sclerosing cholangitis (PSC), was completed in the United States and Canada (HTD1801.PCT003). A total of 55 subjects were treated in this study, and the whole study was divided into three stages: in stage 1 (Week 1-Week 6): HTD1801 1000 mg BID group included 24 subjects, HTD1801 500 mg BID group included 15 subjects, and the placebo group included 16 subjects. In stage 2 (Week 7-12), subjects in the stage 1 placebo group were randomized into the HTD1801 low-dose and high-dose groups; the original treatments group maintained the stage 1 dose regimen; the HTD1801 1000 mg BID group included 29 subjects, and the HTD1801 500 mg BID group included 22 subjects. In stage 3 (Week 13-Week 18), subjects in the two treatment groups were randomized to the maintenance therapy group and the placebo group, including 14 subjects in the HTD1801 1000 mg BID group, 10 subjects in the HTD1801 500 mg BID group, and 26 subjects in the placebo group.

In a single-dose escalation study in Chinese adult healthy subjects, enrollment and administration of all subjects were completed. HTD1801 showed good safety and tolerability in this study, and no serious adverse event (SAE) related to the compound was reported.

1.3 Justification for Study Design

The doses in this study were selected based on the previous clinical data of HTD1801. Studies that have been completed abroad showed that HTD1801 had good safety and tolerability after a single oral dose of 500 mg-4000 mg in healthy subjects (HTD1801.PCT002), and multiple oral doses of 500 mg/day-2000 mg/day in hypercholesterolemic subjects (HTD1801.PCT004). The results of a single-dose Phase I clinical study in healthy Chinese subjects showed that no $\geqslant$ Grade 2 adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) V5.0 after a single oral dose of 500 mg-2000 mg (HTD1801.PCT101). Therefore, since the daily doses of 2000 mg/day (1000 mg BID) and below are reasonable, the maximum dose selected for this study was 2000 mg/day (1000 mg BID).

As shown in the results of a randomized, double-blind, placebo-controlled Phase II clinical study (HTD1801.PCT012) in NASH patients with T2DM completed in the United States, on the basis of maintaining the original blood glucose control treatment in all subjects, the HbA1c levels were significantly decreased in both the HTD1801 500 mg BID group and the HTD1801 1000 mg BID group, i.e., after administration of HTD1801 for 18 weeks, the HbA1c levels were significantly decreased from baseline; compared with the placebo group decreased from 7.0 ± 1.05% to 7.0 ± 1.41%, the HTD1801 500 mg group was decreased from 6.9±0.86% to 6.4±0.65% (p=0.034), and the HTD1801 1000 mg group was decreased from 7.4±1.14% to 6.7±1.27% (p=0.004), showing a significant dose-dependence. Since there are no restrictions on the use of hypoglycemic drugs in subjects, and the expected effective dose of HTD1801 is 1000 mg/day (500 mg BID), the minimum dose of 1000 mg/day (500 mg BID) was selected in this study.

Referring to the clinical routes of administration for BBR and UDCA, and the route of administration in NASH subjects with T2DM established in the United States, the dosing regimen

of BID with meals was applied in this study.

According to the *Guidelines for Clinical studies of Drugs and Biologicals for the Treatment of Diabetes Mellitus* [22], the primary efficacy endpoint in this study was the change in HbA1c from baseline with 12-week treatment. When the scheduled exploratory Phase II clinical study was initiated, guidelines recommend designing an introduction period prior to randomization for education and optimization of dietary and exercise adherence of diabetes mellitus patients. Considering the stability of metabolic control parameters, a 4-week single-blind introduction period was set in this study to accurately evaluate the efficacy of the drug at different doses. In addition, salvage therapy and treatment of hypoglycemia events were determined in accordance with diabetes mellitus-related guidelines and clinical guidelines.

Intestinal flora is the main environmental factor affecting metabolic diseases, and participates in maintaining and regulating the host energy metabolism and immune function. Intestinal flora imbalance may lead to the occurrence and development of chronic diseases, including obesity and diabetes mellitus. In addition, the intestinal flora plays an important role in drug metabolism and can produce metabolites with different activities. Studies are carried out on the changes in intestinal flora with drug intervention to analyze its correlation with diabetes mellitus, which will help to discover the effective components or component groups with definite effects and clear mechanisms of the investigational drug, thereby benefiting the development of new drugs.

1.4 Risk Benefit Assessment

The non-clinical toxicology study on HTD1801 was completed to support this study, including repeated-dose toxicology study, reproductive toxicity study, preliminary carcinogenicity study, preliminary assessment on drug interactions, etc. The results showed good safety and tolerability of HTD1801.

At present, the pharmaceutical study and production of HTD1801 are carried out in accordance with relevant guidelines and regulations with controllable quality. In addition, based on the obtained preclinical study results, it is reasonable to expect that HTD1801 will not cause any unknown or uncontrollable toxic reactions in human. According to the completed phase I clinical studies (HTD1801.PCT002 and HTD1801.PCT004), the drug-related adverse reaction was gastrointestinal discomfort. Drug-related adverse reactions in HTD1801.PCT002 were gastrointestinal discomfort (nausea and abdominal pain); the most common treatment-emergent adverse event (TEAE) in HTD1801.PCT004 study was headache, which may not be related to the investigational drug as judged by the investigator; the severity of the above-mentioned AEs was mostly slight/mild. Two TEAEs were reported in the high-dose group of HTD1801.PCT004: cholecystitis and hepatitis; these two SAE were moderate in intensity and not related to the investigational drug as judged by the investigator.

The completed phase I studies showed good safety and tolerability of HTD1801 in healthy subjects at single oral doses up to 4000 mg, and in subjects with hypercholesterolemia at multiple oral doses up to 2000 mg/day for 28 days. The completed phase II study showed good safety and tolerability of HTD1801 in adult T2DM patients with NASH and adult patients with PSC at multiple oral doses up to 2000 mg/day for 18 weeks. No investigational drug-related SAE were reported (see the Investigator's Brochure for details).

HTD1801 is an ionic salt formed by BBR and UDCA. Both BBR and UDCA have a long history of clinical use in traditional and modern medicine in different countries, with abundant clinical literatures, and their safety is known and controllable. According to previous reports in the literatures, the safety of UDCA has been widely recognized; while BBR has two potential safety issues: exacerbation of jaundice and kernicterus in neonates with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as well injury to the developing fetus in the placenta. BBR can

also be passed through breast milk, which raises some concerns about using BBR while breastfeeding.

For "exacerbation of jaundice and kernicterus in neonates with G6PD deficiency", the clinical indication of HTD1801 is for adult subjects only, so this safety risk dose not exist. In addition, the inclusion/exclusion criteria for the clinical study clearly stipulated those subjects who have any disease that may cause hemolysis or unstable red blood cell count and affect the HbA1c test, such as hemolytic anemia, etc., should not be included in this study.

Based on the results of previous studies, in the clinical studies of HTD1801 completed in the United States, Australia and Canada, the maximum dosing duration are 18 weeks, and female subjects of childbearing potential were included. No drug-related SAEs were observed in these studies. Although developmental toxicity that may cause concern has not been detected in the reproductive toxicity studies that have been completed so far, in order to further ensure the medication safety of subjects, it is necessary to definitely control reproductive risks in the clinical study protocol, including but not limited to the following:

a) Pregnant or lactating female subjects should be excluded; female subjects of childbearing potential are eligible for inclusion in this study only if they are negative in the pregnancy test at screening (V1) and before randomization (V3);

b) Subjects should be strictly screened and take contraceptive according to the study protocol; if the partners of the male subjects or the female subjects are planning to become pregnant, or are unwilling to take reliable contraceptive measures (see APPENDIX 6) during the period from the signing of the informed consent forms (ICFs) to 3 months after the last dose of the investigational drug, the subjects should be excluded;

c) Pregnancies in female subjects of childbearing potential should be followed up throughout the study.

In the inclusion criteria, subjects with hyperglycemia and/or severe acute and chronic complications of diabetes mellitus and severe comorbidities in other organ systems are excluded. During the study, subjects will undergo self-monitoring of blood glucose (SMBG) in addition to following lifestyle intervention requirements and receiving continuous treatment. During the study, the principles of salvage therapy and hypoglycemia event treatment were set up. Subjects with hyperglycemia and repeated episodes of severe hypoglycemia that could not be controlled by salvage therapy can withdraw from the study in advance according to the withdrawal criteria to ensure the safety of the subjects to the greatest extent.

2. STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the effect of HTD1801 on glycemic control in T2DM patients.

2.2 Secondary Objectives

1. To evaluate the safety of HTD1801 in T2DM patients.
2. To evaluate the effect of HTD1801 on improving IR.
3. To evaluate the effect of HTD1801 on fatty liver-related indicators such as liver fat, AST, ALT, ect.
4. To evaluate the effect of HTD1801 on metabolism-related indicators such as body weight, blood lipids, etc.
5. To evaluate the PPK profiles of multiple-dose HTD1801 in T2DM patients, and to provide a reference for determination of the dose in follow-up clinical studies.
6. To evaluate the effect of multiple-dose HTD1801 on the intestinal flora characteristics, and the possible pharmacological effects by acting on the intestinal flora.

3. SUBJECT SELECTION AND WITHDRAWAL

3.1 Inclusion Criteria

Subjects who meet all the following criteria will be included in this study:

1. Male or female subjects who are 18 (inclusive) to 75 (inclusive) years old when signing the ICFs.
2. Subjects who are diagnosed as T2DM according to the WHO criteria 1999.
3. Subjects who have received diet and exercise treatment for ≥8 weeks prior to screening.
4. Subjects whose HbA1c must meet the following criteria:
   (1) Screening (V1) HbA1c: 7.5%≤HbA1c≤11.0% (local laboratory);
   (2) Pre-randomization (V3) HbA1c: 7.0%≤HbA1c≤10.5% (central laboratory).
5. Subjects whose fasting blood glucose must meet the following criteria:
   (1) Screening (V1) fasting blood glucose: <13.9 mmol/L (if the plasma glucose cannot be detected in the local laboratory, the serum glucose result can be accepted);
   (2) Pre-randomization (V3) fasting plasma glucose (FPG): <13.9 mmol/L (central laboratory)
6. At screening, the BMI is within the range of 18-40 kg/m^2 (inclusive).
7. Subjects who agree to maintain the same dietary and exercise habits throughout the study, and are willing and able to properly use a home blood glucose meter for SMBG and record.
8. Subjects who are able to understand and willing to sign the written ICFs and comply with the study protocol.

3.2 Exclusion Criteria

Subjects who meet any one of the following criteria will be excluded from this study:

1. Subjects who have Type 1 diabetes mellitus (T1DM), or specific diabetes mellitus (such as diabetes mellitus due to pancreatic injury, Cushing's syndrome or acromegaly, etc.).
2. Subjects who have diabetic ketoacidosis or hyperosmolar hyperglycemic state within 6 months prior to screening.
3. Subjects who have proliferative retinopathy or macular degeneration, severe diabetic neuropathy, diabetic foot, or intermittent claudication within 6 months prior to screening which are unstable and require treatment.
4. Subjects who have the history of ≥2 episodes of Grade 3 hypoglycemia within 12 months prior to screening (see Section 3.3.1.1 for the definition of hypoglycemia).
5. Subjects who have any disease that may cause hemolysis or erythrocyte instability and affect the HbA1c test, such as hemolytic anemia, etc., at screening (V1).
6. Subjects who have the weight changes (gain or loss) ≥5% before randomization (V3) compared with those at screening (V1).
7. Subjects who have the liver stiffness measurement (LSM) >13.0 kPa measured by liver

transient elastography at screening (V1).

8. Subjects who have used any chemical or traditional Chinese medicines containing UDCA or BBR within 4 weeks prior to screening.
9. Subjects who are known to be allergic to the active ingredients of the investigational drug (HTD1801, BBR, UDCA) or its excipients; or known to be allergic to the salvage drug Empagliflozin or related excipients.
10. Subjects who have the history of drug abuse or dependence within 12 months prior to screening.
11. Subjects who have the refractory urinary tract or genital infection within 6 months prior to screening.
12. Subjects who have severe gastrointestinal diseases at screening (V1) that affect drug absorption, distribution, metabolism, and excretion, including chronic gastrointestinal disease that causes recurrent diarrhea (such as irritable bowel syndrome, ulcerative colitis, Crohn's disease, etc.); or have undergone gastrointestinal surgery that affects drug absorption, such as gastrostomy, anastomosis, or intestinal resection.
13. Subjects who have used insulin or its analogs for more than 2 consecutive weeks within 12 months prior to screening (use of insulin or its analogs for hyperglycemia during pregnancy prior to screening is not within the scope of this limitation);
14. Subjects who have used ⩾2 types of hypoglycemic drugs with different mechanisms prior to screening for more than 8 weeks and within 12 months (use of insulin or its analogs for hyperglycemia during pregnancy prior to screening is not within the scope of this limitation).
15. Subjects who have used any drugs that may affect blood glucose metabolism within 8 weeks prior to screening, such as hypoglycemic drugs (including traditional Chinese medicines indicated for hypoglycemic therapy), systemic glucocorticoids (except for inhalation, eye instillation, and topical skin drugs), growth hormone, non-selective β-receptor blockers (such as propranolol, etc.), thiazide diuretics at a dose of >25 mg/day or aspirin at a dose of >300 mg/day, etc.
16. Subjects who have used liver-protecting drugs (including traditional Chinese medicine) or dietary supplements within 4 weeks prior to screening (see APPENDIX 1).
17. Subjects who have used any chemical drugs, traditional Chinese medicines or dietary supplements for weight loss (see APPENDIX 2), participated in a weight loss program, or followed a special diet within 4 weeks prior to screening.
18. Subjects who have used antibiotics (except for topical application) within 4 weeks prior to screening.
19. Subjects who have been administered with probiotic-containing drugs or dietary supplements within 4 weeks prior to screening or prior to randomization (V3) (see APPENDIX 3).
20. Subjects who have used lipid-lowering drugs at stable doses <4 weeks prior at screening (V1).
21. Subjects who have uncontrolled hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg) at screening (V1) or before randomization (V3).

22. Subjects who have abnormal thyroid function that cannot be controlled with drugs at stable doses, or clinically significant abnormality in thyroid function test results that requires drug treatment at screening (V1).
23. Subjects who have suffered from severe infection (such as acute pancreatitis, COVID-19) or severe trauma, or have undergone major surgery within 3 months prior to screening and are judged to be inappropriate to participate in this study by the investigator.
24. Subjects who have the history of the following acute or chronic liver diseases at screening (V1): autoimmune hepatitis, primary biliary cholangitis, alcoholic liver disease, hepatolenticular degeneration, or drug-induced liver injury.
25. Subjects who have the history of malignant tumors within 5 years prior to screening (except for cured basal cell carcinoma of the skin, carcinoma cervix in situ), or being assessed for potential malignant tumors at screening (V1).
26. Subjects who have the history of psychiatric diseases or are receiving drug treatment, and are judged to be inappropriate to participate in this study by the investigator at screening (V1).
27. Subjects who have had the following history within 12 months prior to screening: Decompensated heart failure (New York Heart Association [NYHA] Class III or IV), unstable angina, myocardial infarction, percutaneous coronary intervention, coronary bypass transplantation, hemorrhagic stroke, and ischemic stroke (except lacunar infarction).
28. Subjects who have clinically significant abnormalities in 12-lead ECG and require treatment or close follow-up (such as Grade II or III atrioventricular block, atrial fibrillation, atrial flutter, pre-excitation syndrome, etc.) at screening (V1); or QT interval corrected by Fridericia formula (QTcF) > 470 ms (male) or QTcF > 480 ms (female) (see APPENDIX 5 for the calculation formula) at screening.
29. Etiological test at screening (V1): positive for hepatitis B surface antigen and hepatitis B viral load (HBV-DNA) above the lower limit of detection of the local laboratory; or positive for anti-hepatitis C antibody and hepatitis C viral load (HCV- RNA) above the lower limit of detection of the local laboratory; or positive for treponema pallidum antibody (TP-Ab); or positive for human immunodeficiency virus antibody (HIV-Ab).
30. Subjects whose laboratory parameters are within any of the following ranges at screening (V1):
    - ALT≥5×ULN, AST≥5×ULN;
    - ALP > 2× ULN;
    - DBIL> 1.5× ULN;
    - TBIL> 1.5× ULN;
    - Serum TG ≥4.52 mmol/L (400 mg/dL), or serum LDL-C >5.69 mmol/L (220 mg/dL);
    - Hemoglobin <1 ×LLN;
    - eGFR < 60 mL/min/1.73 m^2 (see APPENDIX 5 for calculation formula); or urine protein≥++.
31. Subjects who have donated blood or had massive blood loss (≥ 400 mL), or received

blood transfusion or blood products within 3 months prior to screening.

32. Subjects who are alcoholism (14 units of alcohol per week: 1 unit = 285 mL beer, or 25 mL liquor, or 100 mL wine) within the 12 months prior to screening and are unable to control alcoholism during the study.
33. Pregnant or lactating female subjects.
34. Partners of the male subjects or the female subjects are planning to become pregnant, or are unwilling to take reliable contraceptive measures (see APPENDIX 6) during the period from the signing of the ICFs to 3 months after the last dose of the investigational drug.
35. Subjects who have participated in clinical studies on other investigational drugs or medical devices, and taken investigational drugs or used medical devices, or used any unapproved treatment methods within 3 months prior to screening.
36. Subjects who have received vaccines (except inactivated vaccines) within 4 weeks prior to screening or planned to receive the vaccines (except inactivated vaccines) during the study (from the signing of the ICFs to the end of the safety follow-up visit).
37. Subjects who have the medication compliance <80% or >120% in the single-blind introduction period.
38. Subjects who are considered as not suitable for participating in the study by the investigator due to other conditions.

3.3 Withdrawal Criteria

1) Withdrawal decided by the investigator

Withdrawal from the study decided by the investigator means that a subject withdraws from the study when the investigator decides such subject is unsuitable to continue the study due to the following situations during the study, including but not limited to:

- The subject has some comorbidities, complications or deterioration of the condition during the clinical study, and is not suitable to continue the study; or any AEs or clinically significant laboratory abnormality, and is considered as not appropriate to continue participating in the study by the investigator.
- Major protocol deviation. After randomization, the subject dose not meet the inclusion criteria of the study protocol, or does not follow the requirements of the study protocol, and is judged by the investigator that continuing to participate in the study may cause unacceptable risks to the health of the subject.
- The subject does not comply with the treatment regimen of investigational drug and the study follow-up procedures as judged by the investigator (e.g., non-compliance with the medical order in terms of route of administration, study visits, etc.).
- Continued treatment is considered by the investigator to be detrimental to the subject (e.g., pregnancy).
- Withdrawal due to hypoglycemia (see Section 3.3.1 in the protocol).
- Inability to receive hyperglycemia salvage therapy (e.g., subject has a contraindication to the salvage therapy).
- Failure in hyperglycemia salvage therapy (see Section 3.3.2 in the protocol).

- Other conditions considered as not suitable for further participation in this study by the investigator. (Note: The specific reason should be recorded in “Specific Description” of the electronic case report form (eCRF)).

2) Subject's voluntary withdrawal from the study

According to ICFs, if the subject is unwilling to continue participating in clinical study, he/she has the right to withdraw from the study at any time of the study. The subject who withdraws from the study during the screening phase is defined as "screening failure"; the subject who withdraws from the study during the introduction period/before randomization is defined as "randomization failure". During the double-blind treatment phase after randomization, if the subject dose not continue receiving medication and tests therefore is lost to follow-up although he/she does not explicitly propose to withdraw from the study, this subject is also defined as "withdrawal" (or "dropout"). The investigator should learn and record the reasons for withdrawal as much as possible, e.g., the subject consciously feels intolerable to certain adverse reactions, cannot to continue to participate in clinical studies for other reasons, or is lost to follow-up without explaining the reason, etc.

To ensure subject safety, specific criteria for withdrawal from study treatment due to hypoglycemia and failure in hyperglycemia salvage therapy are described in Sections 3.3.1 and 3.3.2.

3) Disposal for subject withdrawal

Investigators must fill in the reason for withdrawal in the eCRF and contact subjects where possible. Subjects who withdraw from the study should return the subject dairy, any remaining investigational drug and packaging of the used investigational drug.

For subjects who fail to be randomized and withdraw early without using the investigational drug after randomization, the safety follow-up visit at 4 weeks after the last dose during the introduction period is not mandatory in this study; if the subjects have AEs at withdrawal, they should be followed up until the events are resolved, unless the subjects are "lost to follow-up" or the events cannot be resolved because of their disease as judged by the investigator.

For subjects who have received at least one investigational drug and withdraw from the study early after randomization, the last dose time should be recorded if possible, and the subjects are recommended to return to the study site for all tests at withdrawal follow-up visit within 1 week of confirmed withdrawal, and to receive the safety follow-up visit at 4 weeks after the last dose. The subjects who withdraw from the study should be followed up until all existing AEs and SAEs are resolved; after subjects discontinue the study treatment, investigators should follow up and report all new AEs and SAEs occurred within 4 weeks after the last dose until the above-mentioned AEs are resolved, unless the subjects are "lost to follow-up" or the events cannot be resolved because of their disease at the investigator’ discretion.

Subjects who withdraw from the study early will not be substituted.

Note: "Lost to follow-up" refers to failure to contact the subject by a minimum of 3 times (each on a different calendar day) with documented method (such as by telephone or email). All attempts should be recorded.

3.3.1 Principles for withdrawal due to hypoglycemia

3.3.1.1 Definition of hypoglycemia

In this study, hypoglycemia is divided into the following categories according to the severity based on the Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020):

Grade 1 hypoglycemia: blood glucose <3.9 mmol/L and ⩾3.0 mmol/L.

Grade 2 hypoglycemia: blood glucose <3.0 mmol/L.

Grade 3 hypoglycemia: Serious event requiring help from others, with altered consciousness and/or physical changes, but no specific blood glucose threshold.

If the subject has the symptoms of hypoglycemia, but is not tested for the blood glucose or has the fingertip or venous blood glucose >3.9 mmol/L, then the subject should not be recorded. The following symptoms may be attributed to hypoglycemia: tremors, hot flashes, dizziness, anxiety, dizziness, palpitations, and hazy vision.

3.3.1.2 Principles for withdrawal due to hypoglycemia

If the subject experiences 1 Grade 3 hypoglycemia during the double-blind treatment phase, and there are no other major causes for hypoglycemia (for example, increased physical activity or missed meals, etc.) other than the investigational drug, then the investigational drug should be discontinued, and the subject will withdraw from this study. The cause for withdrawal should be recorded as "withdrawal due to hypoglycemia", and other anti-diabetic drug treatment will be given by the investigator in accordance with clinical practice.

If the subject experiences 2 ＜Grade 3 hypoglycemia during the double-blind treatment phase, and there are no other major causes for hypoglycemia (for example, increased physical activity or missed meals, etc.) other than the investigational drug, then the investigational drug should be discontinued, and the subject will withdraw from this study. The cause for withdrawal should be recorded as "withdrawal due to hypoglycemia", and other anti-diabetic drug treatment will be given by the investigator in accordance with clinical practice and in compliance with the requirements of the protocol.

If the subject experiences 1 Grade 3 hypoglycemia during the salvage therapy (see Section 5.1.3.3), and there are no other major causes for hypoglycemia (for example, increased physical activity or missed meals, etc.) other than the investigational drug and the salvage therapy drug, then the investigational drug and the salvage therapy drug should be discontinued, and the subject will withdraw from this study. The cause for withdrawal should be recorded as "withdrawal due to hypoglycemia", and other anti-diabetic drug treatment will be given by the investigator in accordance with clinical practice and in accordance with the requirements of the protocol.

If the subject experiences 2 ＜Grade 3 hypoglycemia during the salvage therapy, and there are no other major causes for hypoglycemia (for example, increased physical activity or missed meals, etc.) other than the investigational drug and the salvage therapy drug, then the salvage therapy drug should be discontinued, and the subject will continue to receiving the investigational drug; if the subject has another one hypoglycemia event (Grade 1 or 2 or 3) thereafter, and there are no other major causes for hypoglycemia (for example, increased physical activity or missed meals, etc.) other than the investigational drug, then the investigational drug should be discontinued, and the subject will withdraw from this study. The cause for withdrawal should be recorded as "withdrawal due to hypoglycemia", and other anti-diabetic drug treatment will be given by the investigator in accordance with clinical practice and in accordance with the requirements of the protocol. If the subject has blood glucose level above the hyperglycemia threshold specified in the protocol again after withdrawal of the salvage therapy due to the above hypoglycemia, the investigator can judge whether to start the salvage therapy again or allow the subject to directly withdraw from the study according to the actual conditions.

Subjects should be informed of contacting the study site during self-monitoring in case of:

1) Any episode of hypoglycemia requiring help from others (i.e., Grade 3 hypoglycemia);

2) Any episode of hypoglycemia with fingertip blood glucose <3.9 mmol/L, with or without symptoms.

Note: As described above, subjects will record symptoms and/or fingertip blood glucose measurements they believe to be related to hypoglycemia in the subject diary. Investigators should check the hypoglycemia records in the subject diary, evaluate each episode of hypoglycemia, and carefully inquire about the presence of symptoms during hypoglycemia episode, management, and duration at episode of hypoglycemia. All episodes of hypoglycemia that are judged and confirmed by the investigator must be recorded in the Hypoglycemia Assessment Form of the eCRF.

3.3.2 Principles for withdrawal due to failure in hyperglycemia salvage therapy

3.3.2.1 Hyperglycemia threshold for salvage therapy

If the subject has FPG in line with the following criteria (hyperglycemia threshold for salvage therapy) during the double-blind treatment, with no obvious causes, the subject should contact the investigator in time.

- First 6 weeks of the double-blind treatment phase (including Week 6): FPG≥15.0 mmol/L;
- Week 7-12 of the double-blind treatment phase: FPG≥13.3 mmol/L;

Based on the blood glucose levels reported by the subjects, and combined with the subjects' diet and exercise, the investigator should comprehensively judge whether the subjects need to return to the study site in advance to collect venous blood samples and send them to the central laboratory for collection of FPG test articles. During the study, if the central laboratory results shows that FPG meets the above requirement for the hyperglycemia threshold for salvage therapy, the investigator will decide whether to initiate the hyperglycemia salvage therapy according to clinical practice with comprehensive evaluations.

3.3.2.2 Principles for withdrawal due to failure in hyperglycemia salvage therapy

During the double-blind treatment, when the FPG test result of the subject or the fingertip blood glucose measurement recorded in the subject diary reaches the hyperglycemia threshold for salvage therapy, the investigator should, after learning the results, confirm that subject's poor blood glucose control is caused by the following:

1) The subject fails to adhere to the diabetic diet and exercise lifestyle;
2) The subject has a concurrent disease that may affect blood glucose control;
3) The subject has poor compliance, and dose not take the investigational drug as required.

If the above factors are not present, the investigators should give the subjects the central laboratory test again for FPG within 7 days of being informed of the test results.

If the above factors exist, the investigators should take appropriate measures (such as providing relevant training and education for the subjects), and give the subject a central laboratory test of FPG within 7 days.

Based on the central laboratory FPG results, when the investigator determines that salvage therapy is required, the usage and dosage of the salvage drug (Empagliflozin) will be determined with reference to the Instructions for Use of the drug and diagnosis and treatment guidelines for diabetes mellitus.

Subjects should receive the pre-salvage therapy visit before the salvage therapy. If the subject has contraindications to the salvage therapy, the investigator will arrange the subject to withdraw from the study and conduct a withdrawal visit, and the reason for withdrawal is recorded as "failure to

receive the hyperglycemia salvage therapy".

If the subject has received salvage therapy for 4 weeks during the 12-week double-blind treatment phase, a salvage therapy evaluation visit is required to evaluate the effect of salvage therapy by FPG; if the salvage therapy evaluation visit time (including the visit window) coincides with the routine visit time (including the visit window) during the double-blind treatment phase, they will be pooled into one visit, and the content of the visit should meet the requirements of both visits; the effect of salvage therapy will be evaluated according to FPG . If the subject's FPG does not reach the corresponding hyperglycemia threshold set in the protocol (see Section 3.3.2.1), it is defined as success in salvage therapy, and the subject will continue to use salvage therapy drugs on the basis of the investigational drug according to the protocol. If the subject's FPG reaches the corresponding hyperglycemia threshold set in the protocol (see section 3.3.2.1), it is defined as failure in salvage therapy, and the subject will withdraw from the study, and the reasons for withdrawal are recorded as "Failure in Salvage Therapy". If the subject is receiving salvage therapy at the end of the 12-week double-blind treatment phase, but the salvage therapy duration was less than 4 weeks, the salvage therapy evaluation visit is not required, and the V7 visit is carried out according to the normal procedure.

3.4 Early Termination of Study/Closure of Study Site

The Sponsor has the right to terminate this study at any time, and the Sponsor and the investigator have the right to close the study site at any time. Of course, this situation can only be enforced after mutual agreement. When terminating the study, an independent ethics committee (IEC) and the institutional review board (IRB) must be reported. In the event of early termination of the study or early closure of the study site, all study materials (except for documents that must be retained at site) must be returned to the Sponsor. Investigators must preserve other documents until notified of destruction by the Sponsor. Reasons for early termination of the study or closure of the study site may be, but are not limited to, the following:

- Judgments about the adverse risk-benefit of the investigational drug due to new information, for example:
  - Lack of efficacy of the investigational drug, either in this study or in other studies;
  - Occurrence of a significant previously unknown adverse reaction or a known adverse reaction of unexpectedly higher severity/incidence; or
  - Other adverse safety findings, including clinical examinations and nonclinical manifestations;
- The Sponsor believes that it is unreasonable to continue the above study for medical, ethical, or commercial reasons;
- It is unlikely that the study will be completed within an acceptable time frame due to difficulties in enrollment of subjects;
- Suspension or termination at the request of a regulatory authority.

3.5 Definition of End of Study

End of study is defined as the last visit in which the last subject completed the study plan, unless the end of the study was due to the cause of Section 3.4.

4. STUDY DESIGN

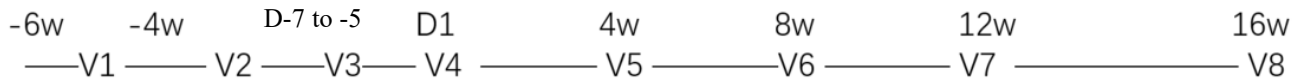
4.1 Study Type and Design Principles

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, proof-of-concept and dose-range finding Phase II clinical study to evaluate the efficacy and safety of 12-week treatment with HTD1801 in T2DM patients.

In this study, 99 subjects are planned to be enrolled and randomized into the investigational drug low-dose group (HTD1801 500 mg, BID), high-dose group (HTD1801 1000 mg, BID) and the placebo group at a ratio of 1:1:1, with 33 subjects in each group. The random stratification factors are controlled attenuation parameter (CAP) and HbA1c, and the random stratification will be conducted based on 1) HbA1c<8.5% and CAP<274 dB/m; 2) HbA1c<8.5% and CAP≥274 dB/m; 3) HbA1c≥8.5% and CAP<274 dB 4) HbA1c≥8.5% and CAP≥274 dB/m.

Each subject should be included in the study for up to 22 weeks, including a screening phase of up to 2 weeks (14 days), a 4-week (28-day) single-blind introduction period, a 12-week (84-day) double-blind treatment phase, and a 4-week (28-day) safety follow-up visit phase of after the last dose.

Screening Phase (up to 2 weeks)	Single-blind introduction period (4 weeks)		Double-blind Treatment Phase (12 weeks)		Safety Follow-up Visit Phase (4 weeks after last dose)
			Dose group	HTD1801 500 mg, BID (N=33)	
				HTD1801 1000 mg, BID (N=33)	
			Control group	Placebo, BID (N=33)	



Schematic Diagram of the Study Design

Screening Phase

Subjects who have signed the ICFs will enter a screening phase of up to 2 weeks, and will complete the required screening tests and be assessed for eligibility for inclusion in this study.

Single-blind Introduction Period

Eligible subjects will first enter the 4-week single-blind placebo introduction period. The investigators will instruct the subjects on lifestyle, medication and SMBG during the introduction period. Subjects will be tested for the relevant indicators again (see the study process) before randomization (V3). For subjects who are eligible according to the protocol before randomization (V3), the HbA1c (7.0%≤HbA1c≤10.5%) tested in the central laboratory before randomization (V3) will be used as the baseline value during the treatment phase; the CAP of liver transient elastography measured at each site will be used as the baseline value.

Double-blind Treatment Phase

On the day of the randomization visit, the inclusion/exclusion criteria of subjects will be reviewed again based on the test results before randomization (V3). Subjects in compliance with the protocol will be randomized into the placebo group, HTD1801 500 mg BID group, and HTD1801 1000 mg BID group at ratio of 1:1:1 based on the central laboratory HbA1c test results (<8.5% and ≥8.5%)

and the CAP (<274 dB/m or ≥274 dB/m) tested by each site before randomization (V3), and enter a 12-week double-blind treatment phase.

The investigators will instruct the subjects on lifestyle, medication and SMBG during the study.

During the study, the subjects will receive the followed-up visit on the specified date once every 4 weeks to evaluate the symptoms and vital signs of the subjects, receive the laboratory tests, and be collected for blood samples for PPK and efficacy endpoints. AEs and concomitant medication, distribution and recovery of investigational drugs, etc. will be recorded.

Safety Follow-up Visit Phase

At the end of the 12-week double-blind treatment phase, all subjects will receive the safety followed-up visit at 4 weeks after the last dose of the investigational drug.

For subjects who have received at least one dose of investigational drug and withdraw the study treatment early after randomization, the subjects are recommended to return to the study site for withdrawal follow-up visit within 1 week after confirmed withdrawal, and to receive the safety follow-up visit at 4 weeks after the last dose of the investigational drug.

4.2 Randomization and Blinding

4.2.1 Randomization method

This randomized, double-blind, placebo-controlled design is applied in this study.

Subjects' random numbers are generated by a randomization statistician nor involved in the study. The randomization statistician uses the SAS 9.4 or above PLAN process to generate the randomization schedule. The subjects are randomly stratified with the block random method and with the quantitatively detected CAP and HbA1c by liver transient elastography as stratification factors, and based on 1) HbA1c<8.5% and CAP<274 dB/m; 2) HbA1c<8.5% and CAP≥274 dB/m; 3) HbA1c ≥ 8.5% and CAP < 274 dB/m; 4) HbA1c ≥ 8.5% and CAP ≥ 274 dB/m; subjects in each site competes for enrollment, and 99 subjects are randomized into the HTD1801 500 mg BID group, HTD1801 1000 mg BID group, and placebo group at 1:1:1.

The random number in this study consists of R+ four digits, where R indicates randomization, the first digit 1 which indicates the stratification factor HbA1c<8.5% and CAP<274 dB/m; 2 indicates the stratification factor HbA1c<8.5% and CAP≥274 dB/m; 3 indicates the stratification factor HbA1c ≥ 8.5% and CAP < 274 dB/m; 4 indicates the stratification factor HbA1c ≥ 8.5% and CAP ≥ 274 dB/m; the last three digits indicate the random serial numbers. This investigational drug will be coded according to the actual quantity of the drug needed and packaged. The drug number and its association with the actual grouping are imported into the Clinflash-IRT system by the drug administrator prior to subject randomization. The subject randomization schedule is imported into the Clinflash-IRT system by the randomization statistician, and the clinical study participants are blinded to the subject randomization schedule.

After the subjects are successfully screened, the subjects are assigned with random numbers and drug numbers by the Interactive Web Response System (IWRS) in accordance with the standard operating procedures of the study site. If subjects who have been randomized, regardless of whether they are administered with the investigational drug, terminate the study for any reason, their random numbers cannot be assigned to other subjects for re-use.

4.2.2 Blinding and blind execution

During the randomized double-blind treatment phase, the packaged investigational drug should be provided in a double-blind manner to maintain the double-blindness of the study. The Sponsor,

investigators, and others involved in the evaluation of subjects and performance the study are unaware of the allocation of the treatment drugs.

The Sponsor or its designated unit will blind the investigational drug and placebo in each test group. Subjects eligible at screening should be administered with the corresponding drug by the investigator according to the drug numbers.

4.2.3 Emergency unblinding principle

The investigators or other clinical observers should not attempt to understand what investigational drug treatment subjects are receiving. If the treatment for the subject must be disclosed for an emergency or rescue, the investigator should contact the monitor, the principal investigator and the Sponsor to jointly decide whether to unblind urgently. In very urgent cases, emergency unblinding can be made at the discretion of the investigators in the site. After the emergency situation is eliminated or controlled, the investigator in the site should notify the monitor, the principal investigator and the Sponsor of the details within 24 hours.

Emergency unblinding is requested by an authorized investigator on the randomization system, and the investigator should record the emergency unblinding person, reason and time.

After emergency unblinding, the investigators can take appropriate measures to treat or take appropriate care based on conventional experiences. Then the subject will withdraw from the stud immediately, and the investigator should record the reasons for withdrawal.

4.3 Study Procedures and Phases

4.3.1 V1: Screening phase (Week -6 to Week -4)

Subjects should arrive at the study site under the fasting condition. The blood samples should be collected under the fasting condition. It is recommended to collect the fasting blood samples at 7:00 ~ 10:00 a.m. Procedures to be completed at V1 include:

- Signing the ICFs;
- Assigning screening number;
- Collecting demographic data, medical history, surgical history, and medication history;
- Measuring body height and body weight to calculate BMI;
- Physical examination;
- Vital signs;
- Etiological test;
- Clinical laboratory tests (blood biochemistry, hematology, urinalysis, coagulation function and thyroid function tests; the specific items included are shown in APPENDIX 7);
- Blood pregnancy test (for female subjects of childbearing age only; see APPENDIX 6 for the definition of "female of childbearing age");
- HbA1c;
- Fasting blood glucose;
- 12-lead ECG;
- Liver transient elastography;

- Guidance on lifestyle;
- Reviewing inclusion/exclusion criteria;
- Recording concomitant medications or treatments;
- Recording AEs;

4.3.2 V2: Single-blind Introduction Period (Week -4)

Procedures to be completed at V2 include:

- Guidance on lifestyle;
- Guidance on the investigational drug during the introduction period (take with meals, BID);
- Distributing the investigational drug for the introduction period (i.e., placebo);
- Distributing the subject diary during the introduction period, and providing guidance such as blood glucose records and medication records;
- Providing SMBG guidance (frequency: measure as required), and guidance on symptoms and management of hyperglycemia and hypoglycemia;
- Recording concomitant medications or treatments;
- Recording AEs;

4.3.3 V3: Single-blind introduction period (Day -7 to Day -5)

Subjects should arrive at the study site under the fasting condition. The blood samples should be collected under the fasting condition. It is recommended to collect the fasting blood samples at 7:00 ~ 10:00 a.m. Procedures to be completed at V3 include:

- Physical examination;
- Vital signs;
- Measuring body weight;
- Clinical laboratory tests (blood biochemistry, hematology, urinalysis, coagulation tests; the specific items included are shown in APPENDIX 7);
- Blood pregnancy test (for female subjects of childbearing age only; see APPENDIX 6 for the definition of "female of childbearing age");
- HbA1c;
- Fasting blood glucose;
- 12-lead ECG;
- Liver transient elastography;
- Abdominal color Doppler ultrasound (kidneys, liver, gallbladder, pancreas, spleen);
- Guidance on lifestyle;
- Viewing SMBG records; providing guidance for the next stage of SMBG;
- Subject diary, recovery and use review of investigational drug: review of the use records of the investigational drug in the introduction period in the subject diary, inquiry for confirmation,

and recovery of the packaging of the used drugs during the introduction period;

- Guidance on the investigational drug: If the subjects do not take the medication according to the protocol, correct guidance should be given;
- Recording concomitant medications or treatments;
- Recording AEs;

4.3.4 V4: Double-blind treatment phase (Day 1)

Subjects should arrive at the study site under the fasting condition. Except for the collection of blood samples for postprandial indicators, the blood samples should be collected under the fasting condition. It is recommended to collect the fasting blood samples at 7:00 ~ 10:00 a.m. Procedures to be completed at V4 include:

- Recovering the remaining investigational drugs and the packaging of used drugs during the introduction period;
- Recovering the subject diary during the introduction period, checking the use records of the investigational drugs during the introduction period, inquiring for confirmation, and calculating the compliance of the subjects taking the investigational drugs during the introduction period;
- Viewing SMBG records;
- Recording concomitant medications or treatments;
- Recording AEs;
- Reviewing inclusion/exclusion criteria;
- Randomization;
- Vital signs;
- PPK blood sample collection (fasting, in the morning);
- Fasting blood glucose, fasting insulin, fasting C-peptide;
- C-reactive protein (fasting);
- Liver function and blood lipid test (LDL-C, HDL-C, TG, TC, AST, ALT, GGT, TBIL, fasting);
- Intestinal flora metabolomics serum samples (fasting);
- Standard meal: see APPENDIX 9 for the detailed process;
- Postprandial blood glucose, postprandial insulin, postprandial C-peptide (0.5 hours postprandial);
- 12-lead ECG;
- Feces sample collection (if any);
- Guidance on lifestyle;
- Guidance on the next stage of SMBG (frequency: 1-2 times a week if there is no abnormality);
- Guidance on the investigational drug: the dosing regimen should be BID with meals during the treatment phase except for QD with dinner on the day of V4 (Day 1);
- Distributing the investigational drug for the treatment phase;

- Distributing the subject diary for the treatment phase.

4.3.5 V5: Double-blind treatment phase (Week 4 [Day 28] ±3 days)

Subjects should arrive at the study site under the fasting condition. The blood samples should be collected under the fasting condition. It is recommended to collect the fasting blood samples at 7:00 ~ 10:00 a.m. Procedures to be completed at V5 include:

- Physical examination;
- Vital signs;
- Body weight;
- Clinical laboratory tests (blood biochemistry, hematology, urinalysis; the specific items included are shown in APPENDIX 7);
- Urine pregnancy test (for female subjects of childbearing age only; see APPENDIX 6 for the definition of "female of childbearing age"); if the urine pregnancy test is positive, a blood pregnancy test should be performed immediately to exclude or verify the pregnancy.
- PPK blood sample collection (within 1 hour before dosing);
- Fasting blood glucose, fasting insulin, fasting C-peptide;
- Liver function and blood lipid test (LDL-C, HDL-C, TG, TC, AST, ALT, GGT, TBIL, fasting);
- 12-lead ECG;
- Viewing SMBG records, and providing guidance for the next stage of SMBG;
- Subject diary, recovery and use review of investigational drug: review of the use records of the investigational drug in the introduction period in the subject diary, inquiry for confirmation, and recovery the remaining investigational drugs and the packaging of used drugs in the previous visit. and assessment of subject compliance;
- Guidance on the investigational drug: If the subjects do not take the medication according to the protocol, correct guidance should be given;
- Recording concomitant medications or treatments;
- Recording AEs;
- Distributing the investigational drug;
- Distributing the subject diary;
- Guidance on lifestyle.

4.3.6 V6: Double-blind treatment phase (Week 8 [Day 56] ±3 days)

Subjects should arrive at the study site under the fasting condition. Except for the collection of blood samples for postprandial indicators, the blood samples should be collected under the fasting condition. It is recommended to collect the fasting blood samples at 7:00 ~ 10:00 a.m. Procedures to be completed at V6 include:

- Physical examination;
- Vital signs;
- Body weight;

- Clinical laboratory tests (blood biochemistry, hematology, urinalysis; the specific items included are shown in APPENDIX 7);
- Urine pregnancy test (for female subjects of childbearing age only; see APPENDIX 6 for the definition of "female of childbearing age"); if the urine pregnancy test is positive, a blood pregnancy test should be performed immediately to exclude or verify the pregnancy.
- PPK blood sample collection (within 1 hour before dosing);
- HbA1c;
- Fasting blood glucose, fasting insulin, fasting C-peptide;
- Liver function and blood lipid indicator test (LDL-C, HDL-C, TG, TC, AST, ALT, GGT, TBIL, fasting);
- Intestinal flora metabolomics serum samples (fasting);
- Standard meal: see APPENDIX 9 for the detailed process;
- Dosing regimen: dosing with meals (in the standard meal process: take the drug immediately after the first bite, and complete the meal after dosing), BID;
- Postprandial blood glucose, postprandial insulin, postprandial C-peptide (0.5 hours postprandial);
- 12-lead ECG;
- Feces collection (if any);
- Viewing SMBG records, and providing guidance for the next stage of SMBG;
- Subject diary, recovery and use review of investigational drug: review of the use records of the investigational drug in the introduction period in the subject diary, inquiry for confirmation, and recovery the remaining investigational drugs and the packaging of used drugs in the previous visit. and assessment of subject compliance;
- Guidance on the investigational drug: If the subjects do not take the medication according to the protocol, correct guidance should be given;
- Recording concomitant medications or treatments;
- Recording AEs;
- Distributing the investigational drug;
- Distributing the subject diary;
- Guidance on lifestyle.

4.3.7 V7: Double-blind treatment phase (or withdrawal visit) (Week 12 [Day 84] ± 3 days or within 1 week of confirmed withdrawal)

Subjects should arrive at the study site under the fasting condition. Except for the collection of blood samples for postprandial indicators, the blood samples should be collected under the fasting condition. It is recommended to collect the fasting blood samples at 7:00 ~ 10:00 a.m. Procedures to be completed at this visit include:

- Physical examination;
- Vital signs;

- Body weight;
- Clinical laboratory tests (blood biochemistry, hematology, urinalysis, coagulation tests; the specific items included are shown in APPENDIX 7);
- Blood pregnancy test (for female subjects of childbearing age only; see APPENDIX 6 for the definition of "female of childbearing age");
- PPK blood sample collection (within 1 hour before dosing);
- HbA1c;
- Fasting blood glucose, fasting insulin, fasting C-peptide;
- Liver function and blood lipid test (LDL-C, HDL-C, TG, TC, AST, ALT, GGT, TBIL, fasting);
- C-reactive protein (fasting);
- Intestinal flora metabolomics serum samples (fasting);
- Standard meal: see APPENDIX 9 for the detailed process;
- Dosing regimen: dosing with meals only in the forenoon on the day of V7 (in the standard meal process: take the drug immediately after the first bite, and complete the meal after dosing);
- Postprandial blood glucose, postprandial insulin, postprandial C-peptide (0.5 hours);
- 12-lead ECG;
- Liver transient elastography;
- Feces collection (if any);
- Viewing SMBG records;
- Subject diary, recovery and use review of investigational drug: review of the use records of the investigational drug in the introduction period in the subject diary, inquiry for confirmation, and recovery the remaining investigational drugs and the packaging of used drugs in the previous visit. and assessment of subject compliance;
- Recording concomitant medications or treatments;
- Recording AEs;
- Guidance on lifestyle.

4.3.8 V8: Safety follow-up visit (Week 16 (Day 112) ± 3 days)

V8 is a telephone follow-up visit to inquire about the occurrence of AEs, and collecting information on concomitant medication and non-drug treatment; if the subject has abnormal results in previous laboratory tests or other tests, the investigator may arrange the subject to receive the test or examination again in the hospital based on the clinical judgment.

4.3.9 Pre-salvage therapy visit

Investigators should give the subjects the central laboratory test again for FPG within 7 days of being informed that the subject's test results have reached the hyperglycemia threshold for salvage therapy (see Section 3.3.2). Subjects whose central laboratory test results meet the hyperglycemia threshold for salvage therapy will receive the pre-salvage therapy visit before the salvage therapy. If the time point between the pre-salvage therapy visits and the follow-up routine visit (V5 or V6) in the double-blind treatment phase is ⩽7 days, the follow-up routine treatment visit (V5 or V6)

is not required. If the subject has contraindications to salvage therapy, the pre-salvage therapy visit is not required, and the subject should withdraw from the study early and receive the withdrawal visit.

The subject should arrive at the study site under the fasting condition. The blood samples should be collected under the fasting condition. It is recommended to collect the fasting blood samples at 7:00 ~ 10:00 a.m. Procedures to be completed at this visit include:

- Body weight;
- Clinical laboratory tests (blood biochemistry, hematology, urinalysis; the specific items included are shown in APPENDIX 7);
- PPK blood sample collection (within 1 hour before dosing);
- HbA1c;
- Fasting blood glucose, fasting insulin, fasting C-peptide;
- Liver function and blood lipid test (LDL-C, HDL-C, TG, TC, AST, ALT, GGT, TBIL, fasting);
- C-reactive protein (fasting);
- Intestinal flora metabolomics serum samples (fasting);
- 12-lead ECG;
- Liver transient elastography;
- Feces collection (if any);
- Guidance on lifestyle;
- Distributing the drug for salvage therapy;
- Recording concomitant medications or treatments;
- Recording AEs.

4.3.10 Salvage therapy evaluation visit (4 weeks after salvage therapy ± 3 days)

If the subject has received salvage therapy for 4 weeks during the 12-week double-blind treatment phase, a salvage therapy evaluation visit is required to evaluate the effect of salvage therapy by FPG; if the salvage therapy evaluation visit time (including the visit window) coincides with the routine visit time (including the visit window) during the double-blind treatment phase, they will be pooled into one visit, and the content of the visit should meet the requirements of both visits; the effect of salvage therapy will be evaluated according to FPG . If the subject's FPG does not reach the corresponding hyperglycemia threshold set in the protocol, it is defined as success in salvage therapy, and the subject will continue to use salvage therapy drugs in addition to the investigational drug according to the protocol. If the subject's FPG reaches the corresponding hyperglycemia threshold set in the protocol, it is defined as failure in salvage therapy, and the subject will withdraw from the study, and the reasons for withdrawal are recorded as "Failure in Salvage Therapy". If the subject is receiving salvage therapy at the end of the 12-week double-blind treatment phase, but the salvage therapy duration was less than 4 weeks, the salvage therapy evaluation visit is not required, and the V7 visit is carried out according to the normal procedure.

The subject should arrive at the study site under the fasting condition. The blood samples should be collected under the fasting condition. It is recommended to collect the fasting blood samples at 7:00 ~ 10:00 a.m. Procedures to be completed at this visit include:

- Physical examination;
- Vital signs;
- Clinical laboratory tests (blood biochemistry, hematology, urinalysis; the specific items included are shown in APPENDIX 7);
- Fasting blood glucose;
- 12-lead ECG;
- Guidance on lifestyle;
- Distributing the drug for salvage therapy;
- Recording concomitant medications or treatments;
- Recording AEs.

4.3.11 Unscheduled visits

Unscheduled visits may be given based on clinical needs. The contents and results of unscheduled visits should be recorded. For all subjects in the Phase II study, efficacy assessments and recordings should be performed according to the visits planned in the study schedule.

5. INVESTIGATIONAL DRUG

5.1 General Information on Drugs

5.1.1 Study products

Investigational Drug

Drug name: HTD1801 Capsules

Dosage form: capsule

Strength: 250 mg/capsule

Appearance: yellow capsule

Expiry date: 18 months (it is tentative and will be revised based on the accumulated data on stability studies)

Storage conditions: stored in a tight container at room temperature.

Supplier: Shenzhen HighTide Biopharmaceutical, Ltd.

Manufacturer: the drug was provided by Shenzhen HighTide Biopharmaceutical, Ltd., and manufactured by the contract manufacturing organization Shanghai STA Pharmaceutical Product Co., Ltd.

Control Drug

Drug name: HTD1801 Placebo Capsules

Dosage form: capsule

Strength: the capsules correspond to the investigational drug strength, but do not contain any active pharmaceutical ingredient.

Appearance: yellow capsules with the same appearance, color and smell as the investigational drug

Expiry date: 18 months (it is tentative and will be revised based on the accumulated data on stability studies)

Storage conditions: Stored in a tight container at room temperature.

Supplier: Shenzhen HighTide Biopharmaceutical, Ltd.

Manufacturer: the drug was provided by Shenzhen HighTide Biopharmaceutical, Ltd., and manufactured by the contract manufacturing organization Shanghai STA Pharmaceutical Product Co., Ltd..

5.1.2 Drug for salvage therapy

Drug name: Empagliflozin

Dosage form: tablets

Strength: 10 mg/tablet

Supplier: Shenzhen HighTide Biopharmaceutical, Ltd.

Storage condition: stored in a well-closed container (according to the instructions for use)

5.1.3 Route of administration

5.1.3.1 Usage and dosage of the investigational drug for the single-blind introduction period:

The placebo should be taken with meals, 4 capsules, BID.

5.1.3.2 Usage and dosage of the investigational drug for the double-blind treatment phase:

500 mg BID dose group: 2 HTD1801 capsules (250 mg/capsule) + 2 placebo capsules should be taken with meals (in the standard meal process on the days of V6 and V7: the drug should be taken immediately after the first bite); the dosing frequency should be BID throughout the double-blind treatment phase, except for QD in the evening on the day of V4 (Day 1), and QD in the morning on the day of V7 (Day 84).

1000 mg BID dose group: 4 HTD1801 capsules (250 mg/capsule) should be taken with meals (in the standard meal process on the days of V6 and V7: the drug should be taken immediately after the first bite); the dosing frequency should be BID throughout the double-blind treatment phase, except for QD in the evening on the day of V4 (Day 1), and QD in the morning on the day of V7 (Day 84).

Placebo group: 4 placebo capsules should be taken with meals (in the standard meal process on the days of V6 and V7: the drug should be taken immediately after the first bite); the dosing frequency should be BID throughout the double-blind treatment phase, except for QD in the evening on the day of V4 (Day 1), and QD in the morning on the day of V7 (Day 84).

5.1.3.3 Salvage therapy

If the subject meets the criteria for initiating the salvage therapy (see Section 3.3.2.1), the salvage therapy should be initiated with Empagliflozin. On the basis of treatment with the investigational drug, the investigator will determine the usage and dosage of Empagliflozin according to the conditions of the subjects, and referring to the instructions for use of Empagliflozin and Diagnosis and Treatment Guidelines for Diabetes Mellitus.

5.2 Drug Packaging and Label

Packaging and labeling of all investigational drugs were performed by Shenzhen HighTide Biopharmaceutical, Ltd. and contract research organizations (CROs) in accordance with terms and applicable national regulations of the Good Clinical Practice (GCP).

The drug label should at least include the following: protocol number, drug number, randomization number, drug strength, drug batch number, expiry date, packaging specification, usage and dosage, storage conditions, and Sponsor name. The label must state “for clinical study use only, please keep out of reach of children”.

5.3 Drug Dispensing, Inventory and Return

The investigational drug used in this study should be provided and handled in accordance with GCPs. The investigational drug-related drugs should be handled by the drug administrators authorized by the clinical study site, including receipt, inventory management, medication, drug recovery, and maintenance related records of each subject. The drug administrators or investigators of the study site should store enough investigational drugs according to the Sponsor's recommendation and distribute them to the subjects. The investigational drug must be distributed as required by the protocol. The investigational drugs are provided free of charge by the Sponsor, and distributed to each study site as scheduled. Special personnel assigned by the clinical study site are responsible for preserving and distributing the drugs.

Investigators and/or drug administrators must record the distribution and return information of all investigational drugs in a timely manner on the drug distribution records, and can distinguish each subject by the random number. The number of drugs dispensed and returned for each subject, the drug number, and the corresponding visit date are recorded in the form. The inventory form is updated synchronously by drug administrators and/or investigators, recording (with dates of receipt or dispensing) incoming, outgoing, and inventory. After the subjects complete the placebo introduction period and are determine to meet the eligibility criteria, eligible subjects will be randomized, and the investigators and/or drug administrators will distribute the drug to the subjects according to the drug numbers assigned by the IWRS. In addition, the investigators and/or drug administrators will inform subjects to return used empty boxes and/or drug packaging bags and/or unused drugs to drug administrators at each follow-up visit.

During the study, the investigators should track the subjects' medication to ensure that the subjects take the investigational drugs properly; and remind the subjects to pay attention to the storage conditions of the drugs. During the study, the investigator should record the number of drugs used by the subjects in detail to determine the medication compliance of the subjects, which is conducive to the correct judgment of the efficacy and safety of the drug. The monitors should count the drugs during the inspection, and the investigational drugs should be used properly. After the drugs are counted during the visit, the drug loss should be recorded in detail in the drug distribution records, and the overdose, missed dose and drug loss should be recorded in the eCRF.

At the end of study, the investigational drug delivery records must be the same as the quantities used and destroyed/returned. Any discrepancies should be recorded and the reason for the discrepancy should be noted.

5.4 Missed Dose

While the subjects are at home, each medication should be recorded in the subject diary, and the subject diary and remaining drugs should be submitted at the follow-up visit for the investigator to review the subject diary and count the remaining quantity and empty packaging of the investigational drug.

In the event of a missed dose, the following rules apply:

- If the missed drug is within 6 h (including 6 h) of the time interval for administration, the investigational drug should be supplemented according to the dose immediately;
- If the missed drug is 6 h out of the time interval for administration, there is no need to supplement the investigational drug;
- Follow-up administration time will be not affected by supplemented administration of the investigational drug.

6. CONCOMITANT/PROHIBITED MEDICATIONS AND TREATMENT

6.1 Concomitant Medication

6.1.1 Allowed concomitant medications/treatment:

Without the consent of the investigator, no other hypoglycemic drugs other than the investigational drug can be used throughout the study, except for the drugs used for the treatment of AEs. Concomitant drugs (such as antihypertensive, lipid-lowering drugs) before the study should continue to be used at their original doses, and the reasons for their use should be fully recorded in the eCRF. Any new concomitant medications/treatments, or changes in concomitant medication doses, and the reason for medication, dates of administration (including start and end dates), and dosing information (including dose, route, frequency) must be recorded in the corresponding section in the eCRF from the signing of the ICFs through the entire treatment phase and during the safety follow-up visit.

6.1.2 Prohibited concomitant medications/treatment:

The following limitations on prohibited concomitant treatments or drugs do not apply to the salvage therapy administered to subjects by the investigator according to the protocol (see Section 5.1.3.3). During the period from the subject signs the ICFs to the end of the double-blind phase (excluding the safety follow-up visit phase and early withdrawal visit), the prohibited concomitant treatments include:

- Any drugs that may affect blood glucose metabolism, such as:
  - Hypoglycemic drugs (including traditional Chinese medicines indicated for hypoglycemic therapy)
  - Systemic glucocorticoids (except inhalation, eye instillation, and topical dermal application)
  - Growth hormone
  - Non-selective β-receptor blockers (such as propranolol, etc.)
  - Thiazide diuretics at a dose > 25 mg/day
  - Aspirin at a dose >300 mg/day
- Thyroid hormones: During the study, no new thyroid hormone drugs or changes in the previous drug regimen (except stable replacement therapy) are allowed.
- Liver-protecting drugs (including traditional Chinese medicine) or dietary supplements (see APPENDIX 1)
- Any chemical drugs, traditional Chinese medicines or dietary supplements for weight loss (see APPENDIX 2), a weight loss program, or a special diet.
- robiotic-containing drugs or dietary supplements (see APPENDIX 3).
- New use of drugs for controlling blood lipid and blood pressure, or changes in previous drug regimens
- Blood transfusion or use of blood products is required.
- Vaccines (except for inactivated vaccines).
- Drugs or treatments that, in the judgment of investigators, may affect the objectivity of the assessment of safety and/or efficacy of subjects in this study.

- Traditional Chinese Medicine.

Unless in emergencies, subjects are prohibited from using any new drug that is not reported during the screening phase without prior consultation with the investigator or self-adjusting the dose of concomitant drugs during the study. In emergencies, if there is a clinical indication for the use of a new drug or dose modification of the concomitant drug, the subject must notify the investigator before using the concomitant drug. The investigator will determine and record any emergency medication's usage, name, dose, route of administration, objectives of treatment, and date of administration.

6.2 Subject Compliance

For the subject with follow-up visits during the study, the "dose to be administered" refers to the total dose of a drug scheduled to be administered by the subject in a certain study phase (e.g., introduction period or treatment phase). For the subject who withdraws from the study early, the "dose to be administered" refers to the dose that should be taken from the beginning of a certain study phase to the day when the investigational drug is administered at the end of this study. Actual dose of the subject: dose dispensed - dose recovered - dose lost (the dose should be checked with the medication records in the subject diary, and the actual medication should be inquired and recorded in detail).

$$\text{Compliance} = \frac{\text{Actual dose of the subject}}{\text{Dose to be administered of the subject}} \times 100\%$$

7. EFFICACY EVALUATION

7.1 Primary Efficacy Endpoint:

Changes in HbA1c from baseline with 12-week treatment.

7.2 Secondary Efficacy Endpoints

1. Percentage of subjects with HbA1c < 6.5% at Week 8 and 12.
2. Percentage of subjects with HbA1c < 7% at Week 8 and 12.
3. Changes in fasting blood glucose from baseline at Week 4, 8, and 12.
4. Changes in postprandial blood glucose from baseline at Week 8 and 12.
5. Changes in fasting insulin level from baseline at Week 4, 8, and 12.
6. Changes in postprandial insulin level from baseline at Week 8 and 12.
7. Changes in fasting C-peptide from baseline at Week 4, 8, and 12.
8. Changes in postprandial C-peptide from baseline at Week 8 and 12.
9. Changes in serum ALT, AST, GGT, and TBIL from baseline at Week 4, 8, and 12.
10. Changes in CAP measured by liver transient elastography from baseline with 12-week treatment.
11. Changes in C-reactive protein from baseline with 12-week treatment.
12. Changes in serum LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), total cholesterol (TC) from baseline at Week 4, 8, and 12.
13. Changes in body weights of subjects from baseline at Week 4, 8, and 12.
14. Changes in medication for blood lipid control in subjects from baseline with 12-week treatment.
15. Evaluation on the PPK parameters of multiple-dose of HTD1801 in T2DM patients.
16. Changes in characteristics of intestinal flora from baseline at Week 8 and 12.
17. Changes in characteristics of intestinal flora metabolites from baseline at Week 8 and 12.

7.3 Safety Indicators

The following indicators need to be recorded for the safety evaluation of the drug:

- AEs
- Hypoglycemia events (see Section 3.3.1.1 for definition of hypoglycemia)
- Clinical laboratory tests
- 12-lead ECG
- Vital signs
- Physical examination

7.3.1 Physical examination

Physical examinations: including skin, mucous membranes, lymph nodes, head, neck, chest,

abdomen, spine/limbs.

7.3.2 Vital signs

Pulse, temperature, sitting blood pressure (systolic and diastolic) measurement. Subjects should be measured at rest. It is recommended that blood pressure be measured on the same arm for each subject at each visit throughout the study.

7.3.3 12-lead ECG

The subject should receive the 12-lead ECG in the supine position after rest. The heart rate, PR interval, QT interval, RR interval, QTcF (see APPENDIX 5 for calculation formula) and QRS complex duration should be recorded. In the event of an abnormal ECG during the visit, the investigator and/or authorized investigator may decide whether to repeat the test based on the subject's clinical condition and evaluate the test results. An unscheduled visit for a 12-lead ECG may also be arranged if clinically indicated.

7.3.4 Clinical laboratory tests

The investigator must evaluate all values outside the normal range (CS: abnormalities with clinical significance, NCS: abnormalities without clinical significance), with signature and date. An AE is recorded only when the CS value judged by the investigator meets the definition of AEs. In the study, the investigator may decide to conduct additional or repeated tests if necessary.

For items (such as hematology) listed in the laboratory test report according to Good Laboratory Practice, but not required in the study protocol, it is no need to record them in the eCRF.

7.3.5 Pregnancy test

Female subjects of childbearing age should receive the blood pregnancy test in local laboratories at V1, V3, and V7 (or withdrawal visit) (see APPENDIX 6). During the study V5 and V6, female subjects of childbearing age should receive the urine pregnancy test in local laboratories, and if the urine pregnancy test is positive, a blood pregnancy test should be performed immediately to exclude or verify the pregnancy. If the V1 blood pregnancy test is positive, the subject will not be able to participate in the study. Female subjects should withdraw from the study immediately once the blood pregnancy test is positive during the study.

7.3.6 Self-Monitoring of Blood Glucose (SMBG)

In the introduction period, investigators should instruct subjects on the precautions for SMBG operation and remind them to record the test results in the subject diary in time as required. During the study, if any problem with the subject's operation or recording is found, repeated or targeted training should be given in time to improve the compliance of the operation.

During this study, subjects should undergo SMBG test under the guidance of the investigator. In case of poor blood glucose control, blood glucose monitoring at corresponding time points can be increased according to the guidance of the investigator. If there are suspected symptoms of hypoglycemia, the blood glucose should be measured as soon as possible; if nocturnal hypoglycemia is suspected, the nighttime self-monitoring of blood glucose should be increased according to the guidance of the investigator. The above blood glucose results should be recorded in the subject diary in time. SMBG procedures are detailed in APPENDIX 10.

7.4 Pharmacokinetic Endpoints

HTD1801 plasma concentration.

The blood volume, processing, transportation and preservation of samples are described in the

central laboratory SOP (see *Laboratory Operation Manual*).

8. ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse events

An Adverse Event (AE) is defined as any untoward medical event that occurs after a subject receives the investigational drug, which may be manifested as symptoms, signs, diseases, or laboratory abnormalities, but may not necessarily have a causal relationship with the investigational drug. Therefore, an AE can be any unfavorable or undesirable symptoms, signs, or diseases, including adverse drug reactions, critical laboratory abnormalities, and diseases during the study.

AEs do not include:

- Diseases, conditions, or laboratory abnormalities that have existed or been detected prior to screening or baseline but not worsen;
- There are no adverse medical events (e.g., hospitalization for elective surgery, social reasons, and/or self-convenience);
- Any medical condition or clinically significant laboratory test abnormality that occurs before the signing of the ICFs and is not related to the study procedures is not considered an AE, and is considered pre-existing.

8.1.2 Hypoglycemia event

The date and time of onset and end of each hypoglycemia event, the classification of hypoglycemia (for the definition of hypoglycemia, see Section 3.3.1.1), blood glucose value and/or description of symptoms, measures taken and description, the determination that whether it is severe hypoglycemia and whether it is resolved, cause and description, the correlation judgment with the investigational drug and the correlation judgment with the salvage therapy drug, etc. should be recorded in detail.

8.1.3 Serious adverse events

A Serious Adverse Event (SAE) refers to an untoward medical occurrence such as death, life-threatening event, permanent or serious disability or loss of function, need for hospitalization or prolongation of hospitalization, and congenital abnormalities or birth defects, after the subject receives the investigational drug; other major medical events: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as major medical events that may not be immediately life-threatening or result in death or hospitalization or may require medical intervention to prevent one of the other outcomes listed in the above definition. such as major treatment in the emergency room or allergic bronchospasm at home, cachexia or convulsions of subjects not hospitalized, drug dependence or addiction, etc.

8.1.4 Suspected unexpected serious adverse reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) refers to a suspected unexpected serious adverse reaction whose nature and severity of clinical manifestations exceed those in the Investigator's Brochure of the investigational drug, the package inserts of the marketed drug or the summary of product characteristics.

Expectedness determination: it should be evaluated according to the related chapters in the Investigator's Brochure (the effective version on the date of the event occurrence) as safety reference information. Unexpectedness refers to an event that is not listed in the Investigator's Brochure or is not listed with the specificity or severity that has been observed for the

investigational drug.

The investigator is responsible for evaluating the relationship between all AEs and the investigational drug. The principal investigator can entrust other qualified clinicians participating in this study to make judgments, but he/she still needs to be responsible for this. The investigator must provide a list of persons who have the corresponding qualifications and accept the commission.

8.2 Causality

The causal relationship between the investigational drug and events can be classified into definitely related, possibly related, doubtfully related, not related, and undecidable.

Definitely related	The AE follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the investigational drug, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure (i.e., the re-challenge test is positive) and other confounding factors such as the fact that original diseases have been ruled out.
Possibly related	The reaction follows a reasonable temporal sequence from administration of the study intervention and follows a known or expected response pattern to the investigational drug, but that could readily have been produced by the subject's clinical state or other treatment methods.
Doubtfully related	The reaction doesn't follow a reasonable temporal sequence from administration of the study intervention, and doesn't follow a known or expected response pattern to the investigational drug, that could readily have been produced by the subject's clinical state or other treatment methods.
Not related	The reaction doesn't follow a reasonable temporal sequence from administration of the study intervention, and follows a known or expected response pattern to non-investigational drug. That could readily have been produced by the subject's clinical state or other treatment methods. The response is resolved when disease is relieved or other treatment methods are stopped. The reaction appears when other treatment methods are reused, and is closely related to other risk factors.
Undecidable	There is no clear temporal sequence relationship between the time of the reaction and the time of drug administration. The reaction follows a similar pattern to the known response pattern of the investigational drug. Same reaction could be produced by other drugs. There is no sufficient basis for judgment.

When the SAE report in this study was further evaluated for compliance with the accelerated reporting criteria for Suspected Unexpected Serious Adverse Reactions (SUSARs), if its causality assessment was "doubtfully related", it was classified as "not related" in the dichotomy.

8.3 Criteria for Determining the Severity of AEs

The severity of AEs should be judged according to the CTCAE 5.0. If there are AEs not listed in the table, the following criteria can be referred to:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL) (instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.);

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self care ADL (self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not

bedridden);

Grade 4: Life-threatening consequences; urgent intervention indicated;

Grade 5: Death related to AE.

Note: The CTCAE terms provide the grading of specific laboratory abnormalities. Grade 4 laboratory abnormality does not automatically indicate a life-threatening event. Abnormal laboratory results still need to be evaluated for AEs.

8.4 Measures Related to Investigational Drug

- Discontinuation - The investigational drug is discontinued due to a specific AE.
- Dose unchanged - No discontinuation of the investigational drug is required for a specific AE.
- Unknown - Only used when the measures to be taken cannot be determined.
- Not applicable – The investigational drug is discontinued for reasons other than a specific AE, e.g.: study was terminated, subject died, the investigational drug was discontinued prior to the occurrence of an AE.
- Dose interruption - The investigational drug is temporarily interrupted (suspended) (including voluntary interruption by the subject) due to a specific AE and following resumption of the drug.

8.5 The Outcome of Adverse Events Can Be Described as The Following:

- Recovered/resolved: "Termination date of (serious) adverse event" should be indicated.
- Recovering/Resolving: The event has not yet been completely resolved, but the subject is already in the recovery phase. Follow-up is needed.
- Unrecovered/Unresolved: The event is in progress.
- Recovered/resolved with sequelae: only if the subject has long-term or lifelong sequelae, such as blindness caused by diabetes and hemiplegia after stroke. "Termination date of (serious) adverse event" should be indicated.
- Fatal: "Termination date of (serious) adverse event" should be indicated. For death caused by AEs, the time of death shall be recorded.
- Unknown: The investigator cannot be informed of the AE, for example, the subject is lost to follow-up.

If the outcome of the AE is assessed as "recovering/resolving", or "unrecovered/unresolved", or "unknown", it is temporarily not necessary to record the termination date of the AE.

If the outcome of the AE is assessed as "recovered/resolved" or "recovered/resolved with sequelae", the termination date of the AE must be recorded.

8.6 Collection, Recording and Reporting of AE

8.6.1 Collection and reporting of AE

AE collection phase

The AEs should be collected since the subject signs the ICFs to participate in the study until the end of 4-week (28-day) safety follow-up visit after the subjects' last dose of the investigational drug. Regardless of its severity, or relationship to the investigational drug, all AEs should be

documented on the appropriate pages of the original medical record and the eCRF.

Adverse medical events that occurred during the screening phase are recorded as the medical history. Adverse medical events in the single-blind introduction period, double-blind treatment phase and safety follow-up visit phase are recorded as AEs; if the severity meets the SAE severity criteria, the adverse medical events are recorded as SAEs.

In order to ensure the safety of the subjects, the investigator should take appropriate measures to track all AEs until the AEs are recovered and stabilized, have other explanations, or the subject is lost to follow-up. This means that observation may still be required after the last visit as specified by the protocol.

Reporting of AEs

At each study visit, the investigator will assess the occurrence of subjective AEs. The investigator can ask a neutral question such as "How have you been feeling since your last visit?". Subjects can report AEs that occur at any other time during the study. All AEs, related or not related to the investigational drug, should be followed up until normal status or remission, or restoration to baseline levels, or the investigator determines that there is no need to continue follow-up, or the subject is lost to follow-up. All AEs will be recorded on the AEs page of the eCRF, regardless of whether the investigator concludes that the event is related to drug treatment.

When reporting an AE, a single diagnosis or syndrome rather than a symptom should be used to describe the AE as far as possible. Investigators should record the onset and end dates of AE symptoms, the severity of AEs and their severity criteria (applicable to SAEs and meet the judgment criteria for SAEs), assessments of the correlation of AEs to the investigational drug or study procedures, measures taken for the investigational drug, the treatment given for AEs and the outcome of AE, etc. in detail.

Subject diaries will not be used as the primary means of collecting AEs. However, if the investigator identifies a potential AE from the information gathered from these documents, the subject should be followed up appropriately for medical evaluation. With this follow-up visit, if a previously unreported AE is identified, such AE should be reported according to the normal reporting requirements.

8.6.2 Collection and reporting of SAEs

For all SAEs that occur within the collection time limit specified in the study protocol, the investigator must fill in the "SAE Report Form" within 24 hours of notification, sign, date, and send it to the Sponsor and Sponsor representative (CRO assigned by the Sponsor) immediately by fax or email (as follows), and appropriate treatment measures should be administered immediately to the subject.

Sponsor email: xielm@hightidetx.com

CRO Email: tipv_hightide@TigermedGrp.com

The investigator should provide detailed and written follow-up reports in a timely manner. For SAE follow-up information, the reporting method is the same as the initial report.

For the reporting of death events, the investigator should provide the Sponsor and the Ethics Committee with required data, such as autopsy report and final medical report.

8.7 Reporting of SUSARs

After the Sponsor and/or Sponsor representative receive safety-related information from any source, they should immediately conduct a comprehensive analysis, evaluation and judgment,

including severity, correlation with the investigational drug, and whether it is an expected event. A expedited report should be made according to the time limit set by the regulatory authority based on the nature (category) of the event. The Sponsor and/or Sponsor representative should submit expedited report of SUSAR to all investigators and study sites participating in the clinical study, the ethics committees, drug regulatory authorities, and health authorities within the prescribed time limit. For specific expedited reporting standards and procedures, please refer to the *Standards and Procedures for the Expedited Reports of Safety Data during Clinical Trials* and *Frequently Asked Questions on Expedited Reporting of Safety Data during Clinical Trials (Version 1.0)* issued by Center for Drug Evaluation (CDE), National Medical Products Administration.

There is no time limit for collection of SAEs judged to be related (definitely related, possibly related, doubtfully related, undecidable) to the investigational drug. This means that investigational drug-related SAEs that occur after the last visit specified in the protocol still need to be reported. The reporting method for SUSAR that occurs after the end of the clinical study and before the approval conclusion is the same as the expedited reporting method before the end of the study.

For the SUSAR report and study-related safety information provided by the Sponsor, the investigator should read them in time, and report them to the study sites and ethics committee.

8.8 Definition of Hospitalization

AEs requiring hospitalization are considered as SAEs. Generally speaking, hospitalization is for admission procedures and treatment, and this AE should be considered as an SAE.

Hospitalizations due to elective surgery, routine clinical procedures, annual check-ups, hospitalization observation or protocol requirements (not due to AEs) are not considered as AEs, but needs to be filled in the clinical evaluation form and included in the eCRF. If an unexpected event occurs during this process, it should be reported as a "serious" or "non-serious" AE according to conventional standards.

Note: Hospitalization or extension of the hospitalization period due to non-medical reasons/convenience reason, etc. or only for clinical study purposes does not meet the criteria for medical events and therefore cannot be regarded as a SAE.

8.9 Pregnancy

If any female subject or partner of a male subject becomes pregnant or is found to be pregnant during the study (from signing the ICFs to within 4 weeks [28 days] after the last dose of the investigational drug), the investigator must record this information in the Pregnancy Event Form and submit it to the Sponsor. The investigator should follow up the pregnancy results until obtaining the pregnancy outcome (e.g., termination of pregnancy, delivery).

If pregnancy outcome meets the criteria for an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, or congenital malformation), the investigator should report it according to the procedure for reporting SAEs.

Other pregnancy outcomes considered as SAEs: "spontaneous abortion", including inevitable and missed abortion.

8.10 Overdose

If the investigator believes that there is a drug overdose (e.g., a single oral dose of more than 4000 mg [16 capsules]) during the clinical study, the investigator should treat the event as a SAE and report it promptly, even if the occurrence is not included in the definition described above. Overdose should be recorded on the AEs page of the eCRF form and noted on the original record.

9. DATA MANAGEMENT

9.1 Data Management Process

The data management of this study should be completed by the CRO data department to ensure the authenticity, integrity, privacy and traceability of clinical study data. Detailed data management procedures will be described in a separate data management plan.

9.2 Data Acquisition

Data will be collected through an electronic data capture (EDC) system. Subject data is entered into the eCRF by the investigator or by an investigator-authorized on-site staff. The investigator or the investigator-authorized staff will receive appropriate training and take appropriate information security measures prior to site start-up or data entry. The investigator should supervise the data collection at the study site. The investigator should ensure that all clinical study data are obtained from clinical study source documents and study records, and are accurate, complete, readable and timely. Source data should be attributable, legible, contemporaneous, original, accurate, complete, consistent, and durable. There should be traces for modification of the source data, without concealing the original data, and the reason for the modification should be recorded.

Unless otherwise specified, eCRF will only be used as a form for collecting data, rather than the raw data. Source documents refer to the original records, documents and data generated in this study, such as hospital medical records, medical images, laboratory records, memos, subject diaries or evaluation forms, drug dispensing records, automatically recorded data from instruments, X-rays, subject's documents, and study-related documents and records kept by pharmacies, laboratories, and medical technology departments, including certified copies. Source documents include source data, which can be present in paper or electronic forms. To avoid differences in assessments between assessors, it should be ensured that the baseline and all follow-up visit assessments of efficacy and safety for the same subject are completed by the same assessor.

The investigator is responsible for maintaining all original documents and ensuring that they are monitored by a clinical research associate (CRA) at each visit. In addition, the investigator should submit a complete eCRF for each subject participating in the study, regardless of the study duration of the subject. All supporting documents (such as laboratory or site records) submitted with the eCRF should be carefully verified for study number and subject number, and all private personal information (including subject names) should be removed or made illegible to protect subjects' privacy.

9.3 Database Design

The eCRF is constructed in the EDC system by the CRO data department, and this process should meet the requirements of Part 11, FDA 21 CFR. The database shall manage data traces, such as system login, data entry, modification, and deletion. The establishment of the database shall adopt the Clinical Data Interchange Standards Association (CDISC) standard as far as possible.

The Sponsor should have written procedures to ensure that changes to the eCRF are necessary, documented, and approved by the investigator. Investigators should keep relevant revision and correction records.

9.4 Data Entry and Change

All input data are in Simplified Chinese. The investigator or the investigator-authorized field staff should fill in and modify the eCRF in accordance with the instructions provided by the CRO data department, while CRA does not have this authority. The investigator should ensure that the data in eCRFs and other reports is accurate, complete, definite and timely. All data should be entered into the EDC during the visit or as soon as possible after the visit, and the data entry should strictly

follow the principle of "what you see is what you record". The EDC must be kept up to date to ensure that it reflects the latest developments in subjects. If certain assessments are not performed during the study, or if certain information is unavailable, inapplicable, or unknown, the investigator or the investigator-authorized field staff should record it in the eCRF.

The data in the eCRF will be handed over to the data server. The investigator must review the data to ensure the accuracy and correctness of all input data, and electronically sign the verified data. The signed information (including the date of signature) will be saved in the audit track and cannot be changed.

The data in the eCRF should be the same as the source document, and if there is any inconsistency, a reasonable explanation should be given. For any corrections or modifications made to the eCRF, the investigator or the investigator-authorized field staff should make the original record legible, keep a rack of the modification, explain the reasons if necessary, and sign and date the modification. Changes to data that have been approved should be re-signed electronically by the investigator.

9.5 Data Verification

According to the finalized data verification plan, the data administrator will set up data logic verification programs in the EDC system.

After the data is entered into the EDC system, the data will be validated by computer logic verification and manual verification to ensure the data is logic, consistent and accurate.

After the data is entered into the EDC system, if there is any data that does not conform to logics, the system logic verification will start operation and trigger a query. These queries should be reviewed and answered by the investigator or the investigator-authorized staff. When the logical verification is no longer valid due to the updated data, the data query should be closed immediately; when the study site confirms the data and provides a reply, the data administrator should review and reply to the information. If the reasons provided by the study site are reasonable, the data query should be closed; if the data problem is not resolved, the data administrator can continue to communicate with the study site by continuing to add the data query until the data problem is finally resolved.

The subject data list/report is generated by programming to support manual data verification throughout the study. When there is data that needs to be clarified/verified/confirmed by the investigator, manual queries can be added to the EDC system, and these queries will be manually closed after the data is corrected or confirmed. The queries will be recorded in the audit track of the EDC system, including the operator's name, time and date.

The data administrator should ensure that all queries are resolved before the database is locked, and the investigator should complete all electronic signatures in the EDC system to ensure the integrity and accuracy of the subject data in the EDC system.

9.6 Medical Coding

The data administrator of the CRO Data Department is responsible for the medical coding for this study. Coding includes medical history, AEs, prior/concomitant medication, and prior/concomitant non-drug therapy.

Prior medical history and AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) (latest version), and submitted in System Organ Class (SOC) and Preferred Terms (PTs). Prior medications and concomitant/concomitant medications, etc., will be coded using the World Health Organization Drug Dictionary (WHO DD) (latest version), all in the Sponsor-confirmed version.

During the coding, any failure in data coding due to improper, inaccurate, and ambiguous medical terminology will be sent to the investigator for verification and confirmation in the form of query by the data administrator.

Before the database is locked, the data administrator will send a medical coding report to the Sponsor for review by the Sponsor.

9.7 Data Locking

After the established database is reviewed and confirmed to be correct, the principal investigator, Sponsor, and statistician will jointly decide to lock the database, and the data administrator will lock the database in the EDC system. In principle, no further changes are allowed to the locked database. If the data that should be modified is found after the data is locked, the database can be modified with approval by the principal investigator, Sponsor, statistician and data administrator, and written records and signatures of all parties should be preserved.

10. STATISTICAL CONSIDERATIONS

10.1 General Principles

All statistical analyses in this study are performed using SAS 9.4 or above statistical software.

The subject information, efficacy data, safety data and other study endpoint data should be statistically described by treatment group. Statistics used include number of cases (missing cases), mean (two-sided 95% confidence interval, if necessary), median, standard deviation, minimum and maximum for consecutive variables; number of cases (missing cases), frequency (two-sided 95% confidence interval, if necessary), percentage, etc. for categorical variables.

Unless otherwise specified, the significance level of the two-sided test is 0.05. The inter-group differences are considered statistically significant if the P for the inter-group comparison is < 0.05.

The missing values in the raw data are not filled, and when the sensitivity analysis of the efficacy and the judgment of the occurrence time of the safety event are performed, the processing method of the missing values in the raw data should be explained in detail in the statistical analysis plan (SAP).

Unless otherwise specified, the baseline is defined as the last valid measurement before the first dose of investigational drug after enrollment.

The statistical analysis plan will be finalized before the database is locked. After the database is locked, the changes in the SAP will be explained in a special section of the statistical analysis report.

10.2 Determination of Sample Size

Assuming a change from baseline in HbA1c of -1.1%, -1.4%, and -0.4%, respectively, with 12-week treatment in the 2 test groups (HTD1801 capsules 500 mg BID, and HTD1801 capsules 1000 mg BID) and placebo group, a pooled standard deviation is 1.1%, and the α level is 0.05 (two-sided). 81 subjects (27 subjects in each group) can provide 90% power to test for the statistical difference between HTD1801 capsules 1000 mg BID and placebo group, and 63% power to test the statistical difference between HTD1801 capsules 500 mg BID and placebo group. Since it is a Phase II exploratory study, alpha correction is not considered. Given the dropout rate of approximately 20%, 99 subjects are planned to be enrolled in the study (33 subjects in each group).

10.3 Statistical Analysis Population

Full analysis set (FAS): According to the principle of Intention to Treat (ITT), including all subjects who have been randomized in the study and used the investigational drug at least once.

Per-protocol set (PPS): Including all subjects in the FAS population with good compliance and no serious protocol violations. FAS and PPS are used in the efficacy analysis.

Safety set (SS): Including all subjects who have been randomized and used the investigational drug at least once following by at least one subsequent safety assessment.

Pharmacokinetic set (PKS): Including all subjects who have been randomized, used the investigational drug at least once and had at least one valid PK measurement.

10.4 Statistical Analytical Procedures

10.4.1 Subject Disposition

The information on subjects who failed in the screening should be described, including the number of cases screened, the number of cases failed in the screening, and the reasons for screening failure.

The number of cases (percentages) are used to describe the subject enrollment, completion, and withdrawal, and the reasons for withdrawing from the study.

The inclusion of subjects into each analysis set should be summarized.

10.4.2 Demographic and baseline characteristics

All demographics and baseline indicator should be analyzed based on the FAS. Demographic variables and baseline characteristics will be summarized by treatment group.

Descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) should be used for continuous variables, and frequencies and percentages should be calculated for categorical variables.

Details will be described in the Statistical Analysis Plan.

10.4.3 Primary efficacy analysis

The efficacy analysis is mainly based on the FAS, and the statistical analysis is based on the PPS. The efficacy analysis is mainly based on the therapy strategy, with the on-treatment strategy as the sensitivity analysis.

The primary efficacy endpoint is the change in HbA1c from baseline with 12-week treatment. For the primary efficacy endpoint, the mixed model repeated measures (MMRM) for repeated measurement data is used for analysis, with the change in HbA1c from baseline as the dependent variable, the treatment group, measurement time point, random stratification factor (CAP$\geqslant$274 dB/m or CAP < 274 dB/m) as the independent variables, and subjects' baseline HbA1c as a covariate. Judgments are made based on model-adjusted least-squares means between-group differences. Sensitivity analysis is performed using an analysis of covariance (ANCOVA) model with the last measurement carried forward (LOCF) for subjects who withdrew from the study before 12 weeks.

10.4.4 Secondary efficacy analysis

Secondary endpoints are as follows:

1. Percentage of subjects with HbA1c < 6.5% at Week 8 and 12.
2. Percentage of subjects with HbA1c < 7% at Week 8 and 12.
3. Changes in fasting blood glucose from baseline at Week 4, 8, and 12.
4. Changes in postprandial blood glucose from baseline at Week 8 and 12.
5. Changes in fasting insulin level from baseline at Week 4, 8, and 12.
6. Changes in postprandial insulin level from baseline at Week 8 and 12.
7. Changes in fasting C-peptide from baseline at Week 4, 8, and 12.
8. Changes in postprandial C-peptide from baseline at Week 8 and 12.
9. Changes in serum ALT, AST, GGT, and TBIL from baseline at Week 4, 8, and 12.
10. Changes in CAP measured by liver transient elastography from baseline with 12-week treatment.
11. Changes in C-reactive protein from baseline with 12-week treatment.
12. Changes in serum LDL-C, HDL-C, TG, and TC from baseline at Week 4, 8, and 12.

13. Changes in body weights of subjects from baseline at Week 4, 8, and 12.
14. Changes in medication for blood lipid control in subjects from baseline with 12-week treatment.

For the measurement data in the secondary efficacy endpoints, the same analysis method as the primary efficacy endpoints is used, with the random stratification factors in the model: CAP and HbA1c; for the enumeration data in the secondary efficacy endpoints, invalid filling is applied and the CMH method is used for inter-group comparison, with the random stratification factors in the model: CAP and HbA1c.

Study Objectives	Endpoints	Estimated Objective
Primary objective: to evaluate the effect of HTD1801 on glycemic control in T2DM patients.	Primary endpoint: changes in HbA1c from baseline with 12-week treatment.	**Primary Estimated Objective** Population: according to the ITT principle, including all subjects who have been randomized in the study and used the investigational drug at least once. Therapy: randomly assigned therapy (see Section 4.1 for details) and possible salvage therapy (see Section 3.3.2 for details) Endpoint: see the left column Concomitant event and treatment strategies: for concomitant event of the salvage therapy, the therapy strategy should be applied, i.e., the data after salvage therapy should also be included in the analysis Summary at population level: the least-squares means inter-group differences should be calculated using MMRM and the ANCOVA model of LOCF (see Section 10.4.3 for details) **Secondary Estimated Objective** Population: according to the ITT principle, including all subjects who have been randomized in the study and used the investigational drug at least once Therapy: randomized therapy (see Section 4.1 for details) and possible salvage therapy (see Section 3.3.2 for details) Endpoint: see the left column Concomitant event and treatment strategies: for concomitant event of the salvage therapy, the on-treatment strategy should be applied, i.e., the data after salvage therapy should also be included in the analysis Summary at population level: the least-squares mean inter-group differences should be calculated using MMRM and the ANCOVA model of LOCF (see Section 10.4.3 for details)
	Secondary measurement endpoints: see Section 10.4.4 for details.	**Primary Estimated Objective** Population: according to the ITT principle, including all subjects who have been randomized in the study and used the investigational drug at least once. Therapy: randomly assigned therapy (see Section 4.1 for details) and possible salvage therapy (see Section 3.3.2 for details) Endpoint: see the left column Concomitant event and treatment strategies: for concomitant event of the salvage therapy, the therapy strategy should be applied, i.e., the data after salvage therapy should also be included in the analysis Summary at population level: the least-squares means inter-group differences should be calculated using MMRM and the ANCOVA model of LOCF (see Section 10.4.3 for details) **Secondary Estimated Objective** Population: according to the ITT principle, including all subjects who have been randomized in the study and used the investigational drug at least once Therapy: randomized therapy (see Section 4.1 for details) and possible salvage therapy (see Section 3.3.2 for details) Endpoint: see the left column Concomitant event and treatment strategies: for concomitant event of the salvage therapy, the on-treatment strategy should be applied, i.e., the data after salvage therapy should also be included in the analysis

		Summary at population level: the least-squares means inter-group differences should be calculated using MMRM and the ANCOVA model of LOCF (see Section 10.4.3 for details)
	Secondary metric endpoints: see Section 10.4.4 for details.	**Primary Estimated Objective** Population: according to the ITT principle, including all subjects who have been randomized in the study and used the investigational drug at least once. Therapy: randomly assigned therapy (see Section 4.1 for details) and possible salvage therapy (see Section 3.3.2 for details) Endpoint: see the left column Concomitant event and treatment strategies: for concomitant event of the salvage therapy, the therapy strategy should be applied, i.e., the data after salvage therapy should also be included in the analysis Summary at population level: CMH method is used after invalid filling applied to calculate inter-group differences (see Section 10.4.3 for details) **Secondary Estimated Objective** Population: according to the ITT principle, including all subjects who have been randomized in the study and used the investigational drug at least once. Therapy: randomly assigned therapy (see Section 4.1 for details) and possible salvage therapy (see Section 3.3.2 for details) Endpoint: see the left column Concomitant event and treatment strategies: for concomitant event of the salvage therapy, the on-treatment strategy should be applied, i.e., the data after salvage therapy should also be included in the analysis Summary at population level: CMH method is used after invalid filling applied to calculate inter-group differences (see Section 10.4.3 for details)
Safety endpoints	Safety endpoints: see Section 10.4.5 for details.	**Estimated Objective** Population: including all subjects who have been randomized and used the investigational drug at least once following by at least one subsequent safety assessment. Therapy: actually assigned therapy and possible salvage therapy (see Section 3.3.2 for details) Endpoint: see the left column Concomitant event and treatment strategies: for concomitant event of the salvage therapy, the therapy strategy should be applied, i.e., the data after salvage therapy should also be included in the analysis Summary at population level: the incidence is calculated for safety endpoints, and the chi-square test is used (Fisher's exact test is used based on the data) for inter-group comparison if necessary.

10.4.5 Safety data analysis

Based on the SS, the safety analysis is performed based on the therapy strategy.

AEs

All AEs are coded by MedDR SOC and PT. The number and percentage of AEs, such as AEs, drug-related AEs, SAEs, and other major medical events, are calculated separately, and a detailed list is provided. The incidence is calculated with the number of subjects in SS in each group as the denominator, and the chi-square test is used (Fisher's exact probability method is used based on the data) for inter-group comparison if necessary.

Hypoglycemia event

The number of subjects, percentage and number of cases of hypoglycemia events (Grade 1 hypoglycemia event, Grade 2 hypoglycemia event, Grade 3 hypoglycemia event, etc.) are analyzed.

Clinical laboratory tests

Including hematology, blood biochemistry, urinalysis and coagulation tests.

The visit results of each laboratory test and their changes from baseline are described with mean, standard deviation, median, minimum and maximum.

The clinical judgment results (normal, abnormal with no clinical significance, abnormal with clinical significance, and not tested) of the laboratory results before and after treatment are presented in cross tabulation.

For subjects with abnormal laboratory results during the double-blind treatment phase, the results of each examination and judgment are listed according to the abnormality with clinical significance and the abnormality without clinical significance.

Evaluation on vital signs

The results of vital signs in each visit each and their changes from baseline are described with mean, standard deviation, median, minimum and maximum.

Evaluation on physical examination

The physical examination results of each visit are described, the number of normal and abnormal subjects and percentages are calculated, and abnormal values are listed.

Evaluation on ECG

Refer to the evaluation of laboratory test indicators.

10.4.6 Pharmacokinetic analysis

The data on blood samples collected in the morning under fasting conditions on V4, and before the first dose of on the day of V5, V6, and V7 are summarized to evaluate the trough concentration of multiple-dose HTD1801 in T2DM subjects, and descriptive statistics of the trough concentration are performed.

10.4.7 Population pharmacokinetic analysis

See the separate PPK analysis plan for details.

10.4.8 Intestinal flora analysis

For details, see the separate analysis plan for intestinal flora.

11. CLINICAL STUDY MANAGEMENT

11.1 Statement

This clinical study will be conducted in accordance with the standard operating procedures of the Sponsor and CRO, to ensure that the study complies with the *Declaration of Helsinki, E6 Guidelines for Good Clinical Practice* issued by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), *NMPA GCP*, and clinical study regulations.

When the investigator signs the protocol, he agrees to conduct the study in strict accordance with the protocol, GCP, and relevant laws and regulations, and keep all the information provided by the Sponsor in accordance with confidentiality requirements.

11.2 Ethical Part

This study is designed and prepared on the basis of the *Declaration of Helsinki* by the World Medical Association, taking into account the rights and welfare of the subjects. Principal investigator or investigators of the study should explain the objectives of the study and all potential possibilities to the subject. Only subjects who voluntarily agree to participate in the clinical study and sign the ICFs can be enrolled.

Investigators and researchers participating in the study should correctly understand and be familiar with the study protocol, and be able to prepare measures in advance, such as response measures for SUSAR, required reports and adequate training. Clinical investigators must comply with the *Declaration of Helsinki*, *E6* issued by ICH, GCP issued by NMPA and relevant regulations.

Principal investigator and the personnel participating in the study should abide by the study protocol to conduct the study scientifically with the currently recognized technology.

According to the policies and regulations of China, investigators need to provide relevant documents to the ethics committee.

Before the start of the clinical study, the approval from the ethics committee and the drug regulatory authority must be obtained.

The modification of the study protocol needs to be submitted to the ethics committee for approval, and the drug regulatory authority should be notified according to local requirements.

For any clinical safety-related SAE or SUSAR during the clinical study that may affect the safety of the subjects and the implementation of the study, the investigator must inform the Ethics Committee.

The completion of the study should be notified to the ethics committee.

11.3 Original Record Verification

The investigator must properly handle all data obtained during clinical study to ensure the rights and privacy of subjects included in clinical study. The investigator must agree to the CRA/auditor/inspector to view and review the required clinical study data in order to verify the accuracy of the raw data and understand the study schedule. If the original records cannot be verified, investigators should agree to assist the monitors/auditors/inspectors to further confirm the quality control of the data.

11.4 Quality Assurance and Audit

All drugs and materials used in the study are premised on the basis of quality control. The Sponsor and authorized personnel or related medical regulatory authorities have the right to review the

study, the purpose of which is to ensure the authenticity of clinical study data and the compliance with the study protocol.

This study will be organized, carried out and reported in accordance with the study protocol and standard operating procedures of the Sponsor and CRO. In ICH E6, quality assurance (QA) is defined as "All planned and systematical actions that are established to ensure that the study is performed and the data are generated, documented (recorded), and reported in compliance with GCP and applicable regulatory requirement(s)". The Sponsor’s QA work will be carried out in accordance with the study audit plan. Section 5.19.3(b), ICH E6 states that the audit plan and the study audit process should be established under the governance by the importance of the study in the submissions to the competent authority, the number of subjects included in the study, study type and complexity, the risk level to subjects in the study, and any issues identified. QA work can be outsourced to a CRO or an independent consultancy. Investigators are required to support the audit, attend the audit activities as required by the auditor, and allow the auditor to directly access the original data/documents, including all medical records, study-related documents and mails, and the informed consent documents of the study. Subjects will be informed of the inspection or audit process of the study, but their privacy and data will be strictly protected.

11.5 Informed Consent Form (ICF)

Investigators are responsible for explaining to each subject the purpose, methods, benefits and potential risks of the study, alternative treatment methods, rights and obligations of subjects in accordance with the *Declaration of Helsinki*; subjects should be informed that they have the right to withdraw from the study at any time without compromising their personal interests. ICFs signed by the subject must be obtained before any operating procedures related to the study.

Oral explanations must be made when giving written ICFs to subjects. The ICFs must be dated and signed by each subject or his/her legal guardian or impartial witness. The signed ICF (including information page) should be kept by the subject in duplicate, and the other signed ICF should be kept by the study site as a study file.

The ICFs must be agreed and signed by the subjects or their legal guardian or impartial witness before any study-related process begins. Before obtaining the ICFs, investigators or their designees should provide subjects with sufficient time and opportunity to ask for details about the study and to decide whether to participate in the study. The informed consent process should be documented in the course record or study medical record on the day of the screening visit.

The investigator is responsible for the informed consent process. If any information about the subject's willingness to continue participating in the study is obtained during the study, the ICFs must be updated and given to the subject to confirm the subject's willingness to continue participating in the study. The revised ICFs should be provided to subjects with the ethical approval.

By signing the ICFs, the subject must also agree to allow the Sponsor, the NMPA, the auditor and/or the clinical study monitor authorized by the Sponsor to access the raw data of the study. Reviewers must abide by the confidentiality statement.

11.6 Modification of Study Protocol

After the protocol is approved by the Ethics Committee, if the protocol is amended during the implementation process, such amendment should be implemented with the approval from the Ethics Committee.

Any amendments to the protocol, major or non-major protocol amendments, are required to be made in writing. Substantial protocol amendments that definitely affect the safety of subjects, the scope of the study, or the scientific quality of the study should be approved by the Ethics

Committees of all sites. In order to protect the safety of all subjects in the study, the above requirements should not prevent the investigator or Sponsor from taking any urgent measures. If the investigator believes that the protocol must be amended immediately for safety reasons, the investigator should notify the Sponsor's designated institution in a timely manner, and inform the Ethics Committee of the study site in accordance with the policies formulated by the Ethics Committee that approved the study, local regulations and policies. Any changes that only affect the study management do not require substantial protocol amendments or approval from the Ethics Committee, but these changes must be notified to the Ethics Committee. In these cases, the Sponsor will send an official letter to the Ethics Committee detailing the changes.

11.7 Protocol Deviation

The investigators should carry out this clinical study according to the clinical study protocol approved by the Ethics Committee and in accordance with GCPs. The protocol is established to enable investigators to comply with Section 4, ICH E6. During the study, the investigator should not deviate from the protocol unless urgent measures are taken to eliminate the direct harm to the subjects. In the event of other unexpected circumstances that require deviation from the procedures specified in the protocol, the investigator should consult with the medical monitor (and the Ethics Committee, if necessary) to determine appropriate measures.

The study site should record all protocol deviations, including but not limited to, the time of the protocol deviation, the time of discovery, the description of the event and the measures taken. In case of serious protocol deviation, the study site should promptly notify the medical monitor, CRA, and Ethics Committee.

11.8 Case Report Form

The CRO database programmer will create an eCRF on the EDC system, and in eCRF, only appropriate identification codes (such as site number and subject number) and initials are used to identify different subjects. eCRF is used to record the clinical study data of subjects and is an integral part of the study and related study reports. Therefore, the input must be accurate and complete. eCRF is maintained in the EDC system by the investigator or the investigator-authorized staff (indicated in the study authorization form). All data input must be completed and stored. The investigator must declare the authenticity of all information in the eCRF through an electronic signature.

During the clinical study, eCRF must be completed after each visit to record subjects' conditions.

Medical history records and other records related to subjects' disease progression during the study are kept by the investigator. These records should contain: original or photocopy of laboratory data and other medical test results (such as ECG). These data must be kept in the study site together with subjects' medical records.

11.9 Monitoring

The Sponsor or the CRO entrusted by the Sponsor shall conduct the monitoring.

Before a site is selected for the study, a site selection visit will be conducted to confirm that the site, equipment, and staff meet the requirements of the protocol and GCP.

During the study, on-site monitoring at the study site is carried out by the monitor at regular intervals. For each monitoring, the date of the visit should be recorded in the Visit Record Form of the study site. The site monitoring will be accepted by the Sponsor depending on the study quality.

The study monitoring activities by the monitor include:

- The monitor should initiate the visits at the study site, collect and distribute necessary pre-study documents; give instructions to the investigators and site staff on the protocol, study procedures and expectations; obtaining assurances that investigators will conduct the study in accordance with study requirements and GCPs, and introducing study materials to investigators and corresponding study staff.
- Monitoring visits: As required by the GCP, monitors participating in the current study should be fully informed about confidentiality issues and compare data in the eCRF with data from hospital or clinical records (raw data). Before the study, the monitor should discuss with the investigator the specific items required as raw data, determine the nature and location of all raw data, and ensure that the Sponsor or investigator is aware of the source of the raw data used to complete the eCRF, and the inspection and verification authorities of the monitor authorized by the Sponsor; all observations and findings during the monitoring process must be verifiable. If electronic records are kept in the Study Institution, the verification method must be discussed with the study member.

Raw data must be available to demonstrate at least:

- Subject identity, eligibility and participation in the study;
- Appropriate informed consent procedures;
- Date of visit;
- Records of safety and efficacy parameters;
- Adequate reporting and visits of AEs;
- Concomitant medications and treatment;
- Drug receipt/dispensation/return records;
- Information on administration of the investigational drug;
- Subject's completion of treatment, discontinuation of treatment, or withdrawal from the study, with appropriate reasons;
- The data is true, accurate and complete;
- The safety and rights of subjects are protected;
- Investigator implementation complies with currently approved protocol, GCPs and all relevant regulatory requirements.

The objectives of monitoring include:

- Check and evaluate study schedule;
- Review the study data collected;
- Implement the source document verification process;
- Identify any problems and develop solutions.

During the study, the monitor should have direct access to all relevant documents with the consent of the investigators, and the investigators should ensure that they and the relevant investigator will meet the monitor regularly to discuss the findings of the visit and any related issues.

11.10 Intellectual Property

All information obtained from the Sponsor is regarded as the Sponsor's intellectual property. Therefore, investigators and all other relevant personnel must keep the information confidential and shall not disclose it to a third party without the Sponsor's prior consent.

11.11 Subjects' Privacy

Investigators must maintain the privacy of subjects. In all the documents submitted to the Sponsor, only the screening number/randomization number and initials of subjects can be used to identity them, and their names should not be indicated. Investigators must keep the private information such as names and addresses of subjects strictly confidential and cannot submit them to the Sponsor.

12. PUBLICATIONS

The ownership of the study results remains with the Sponsor. The investigators should guarantee not to publish or release any content related to the study and/or study results by journal publications, academic or commercial conferences without the written permission of the Sponsor. Regarding the manuscript and publication, the Sponsor makes the final decision. In addition, the investigators should be aware that the Sponsor will not withhold permission to publish without reason after communication.

To prevent inadvertent disclosure of confidential information or unprotected inventions, the investigators must notify the Sponsor in advance, consult with, or review any planned publications or release in other form (publication/release forms include, but are not limited to, journal articles, posters, guest lecture, etc.). The Sponsor may require the investigators to delete any previously unpublished confidential information prior to publications.

13. DATA STORAGE

13.1 Source Data and Source Documents

In this study, the source data includes records of clinical findings, observations, and other related activities for reconstruction and evaluation of the study. The raw data is contained in the source documents.

The source documents involved in the study are original records, documents and data (such as hospital medical records, medical images, laboratory records, memos, subject diaries or evaluation forms, drug dispensing records, automatically recorded data from instruments, microfilm, photographic plates, X-rays, subject's documents, and study-related documents and records kept by pharmacies, laboratories, and medical technology departments, including certified copies, ect.). The source documents must be retained to support the information provided in the eCRF.

13.2 Data Storage in Study Sites

13.1.1 Data related to the Ethics Committee

The personnel responsible for data storage in the study site must keep the minutes and abstracts of the Ethics Committee meetings until 5 years after the study is suspended or completed. If the Sponsor wishes to keep it for a longer period of time, both parties will discuss and decide on the storage time and method. The personnel responsible for data storage or the investigator needs to contact the Sponsor if any changes made by the study site to the data storage.

13.1.2 Data related to the implementation of the study

The personnel responsible for data storage in the study site must keep the following documents until 5 years after the investigational drug is approved for marketing. If the Sponsor wishes to keep it for a longer period of time, both parties will discuss and decide on the storage time and method. The personnel responsible for data storage or the investigator needs to contact the Sponsor if any changes made by the study site to the data storage.

- Raw data
- Original or copy of the study contract, ICFs, and other GCP-related materials provided by the study site staff;
- Study protocol, GCP-related materials from the Ethics Committee, or GCP-related materials from other sources;
- Records of investigational drug management and other records related to study implementation.

13.3 Data Storage by The Sponsor

The Sponsor will keep the following materials (including documents and data) until 5 years after the investigational drug is approved for marketing. According to relevant regulations, a longer storage time may be required. It is the Sponsor's responsibility to inform the investigator/study site of when the data is no longer necessary to be kept.

- The original or copy of study protocol, study contract, and study report, or GCP-related materials provided by the Sponsor;
- Case report form, GCP-related notice, or GCP-related materials from the investigator;
- Records of monitoring and audit, or other related operation records;

- Data obtained during the study;
- Relevant records required by GCP.

14. REFERENCES

[1] Wan Xingyi, Li Ling. New progress in drugs for type 2 diabetes mellitus [J]. Medical Review, 2014, 20(22): 4133-4135.

[2] Guidelines for prevention and treatment of type 2 diabetes mellitus in China (2013 Edition) [J]. Chinese Journal of Diabetes, 2014, 22(08):2-42.

[3] Guidelines for prevention and treatment of type 2 diabetes mellitus in China (2017 Edition) [J]. Chinese Journal of Diabetes, 2018,10(01):4-67.

[4] Guidelines for prevention and treatment of non-alcoholic fatty liver disease (updated in 2018) [J]. Journal of Practical Hepatology, 2018, 21(02): 177-186.

[5] Hu Shanlian, Liu Guoen, Xu Zhangrong, et al. Research status of diabetes epidemiology and disease economic burden in China [J]. China Health Economics, 2008, 27(8): 5-8.

[6] Yan Dewen, Xiao Xinhua. Expert consensus on graded diagnosis/treatment and quality management of type 2 diabetes mellitus [J]. Chinese Journal of Medical Frontiers (Electronic Edition) 2020, Volume 12, Issue 5, Pages 38-53, ISTIC, 2020.

[7] Dong H, Wang N, Zhao L, Lu F. Berberine in the treatment of type 2 diabetes mellitus: a systemic review and meta-analysis. Evid Based Complement Alternat Med. 2012;2012:591654.

[8] Chang W, Chen L, Hatch GM. Berberine as a therapy for type 2 diabetes and its complications: From mechanism of action to clinical studies. Biochem Cell Biol. 2015 Oct;93(5):479-86.

[9] Jun Yin, Jianping Ye, Weiping Jia. Effects and mechanisms of berberine in diabetes treatment. Acta Pharmaceutica Sinica B. 2012;2(4):327-334.

[10] Zhou J, Zhou S, Tang J, Zhang K, Guang L, Huang Y, Xu Y, Ying Y, Zhang L, Li D. Protective effect of berberine on beta cells in streptozotocin- and high-carbohydrate/high-fat diet-induced diabetic rats. Eur J Pharmacol. 2009 Mar 15;606(1-3):262-8.

[11] Pang B, Zhao LH, Zhou Q, Zhao TY, Wang H, Gu CJ, Tong XL. Application of berberine on treating type 2 diabetes mellitus. Int J Endocrinol. 2015;2015:905749.

[12] Zhang H, Wei J, Xue R, Wu JD, Zhao W, Wang ZZ, Wang SK, Zhou ZX, Song DQ, Wang YM, Pan HN, Kong WJ, Jiang JD. Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. Metabolism. 2010 Feb;59(2):285-92.

[13] Shima KR, Ota T, Kato KI, Takeshita Y, Misu H, Kaneko S, Takamura T. Ursode-oxycholic acid potentiates dipeptidyl peptidase-4 inhibitor sitagliptin by enhancing glucagon-like peptide-1 secretion in patients with type 2 diabetes and chronic liver disease: a pilot randomized controlled and add-on study. BMJ Open Diabetes Res Care. 2018 Mar 17;6(1):e000469.

[14] Zheng X, Chen T, Jiang R, Zhao A, Wu Q, Kuang J, Sun D, Ren Z, Li M, Zhao M, Wang S, Bao Y, Li H, Hu C, Dong B, Li D, Wu J, Xia J, Wang X, Lan K, Rajani C, Xie G, Lu A, Jia W, Jiang C, Jia W. Hyocholic acid species improve glucose homeostasis through a distinct TGR5 and FXR signaling mechanism. Cell Metab. 2020 Dec 17:S1550-4131(20)30652-5.

[15] Mahmoud AA, Elshazly SM. Ursodeoxycholic acid ameliorates fructose-induced metabolic syndrome in rats. PLoS One. 2014 Sep 9;9(9):e106993.

[16] Murakami, M., Une, N., Nishizawa, M. et al. Incretin secretion stimulated by ur-sodeoxycholic acid in healthy subjects. SpringerPlus 2, 20 (2013).

https://doi.org/10.1186/2193-1801-2-20.

[17] Mitsuyoshi H, Nakashima T, Sumida Y, Yoh T, Nakajima Y, Ishikawa H, Inaba K, Sakamoto Y, Okanoue T, Kashima K. Ursodeoxycholic acid protects hepatocytes against oxidative injury via induction of antioxidants. Biochem Biophys Res Commun. 1999 Sep 24;263(2):537-42.

[18] Lukivskaya O, Patsenker E, Buko VU. Protective effect of ursodeoxycholic acid on liver mitochondrial function in rats with alloxan-induced diabetes: link with oxida-tive stress. Life Sci. 2007 Jun 6;80(26):2397-402.

[19] Ishizaki K, Iwaki T, Kinoshita S, Koyama M, Fukunari A, Tanaka H, Tsurufuji M, Sakata K, Maeda Y, Imada T, Chiba K. Ursodeoxycholic acid protects conca-navalin A-induced mouse liver injury through inhibition of intrahepatic tumor ne-crosis factor-alpha and macrophage inflammatory protein-2 production. Eur J Pharmacol. 2008 Jan 6;578(1):57-64.

[20] Sun, L., Xie, C., Wang, G. et al. Gut microbiota and intestinal FXR mediate the clinical benefits of metformin. Nat Med 2018; 24:1919-1929.

[21] Ashby K, Navarro Almario EE, Tong W, Borlak J, Mehta R, Chen M. Review article: therapeutic bile acids and the risks for hepatotoxicity. Aliment Pharmacol Ther 2018;47:1623-1638.

[22] Guidelines for Clinical studies of Drugs and Biologicals for the Treatment of Diabetes Mellitus

APPENDIX 1: Hepatoprotective Drugs

Hepatoprotective drugs commonly used in clinical practices include but are not limited to the following:

Type	**Drug Name**
Hepatocyte Membrane Repair and Protective Agents	Hepatocyte growth-stimulating hormone, polyene phosphatidylcholine, etc.
Alexipharmacons	Glutathione, N-acetylcysteine, tiopronin, penicillamine, etc.
Enzyme-lowering Hepatoprotective Drugs	Bifendatatum, bicyclol, etc.
Choleretic Drugs	Ademetionine, ursodeoxycholic acid, anethole trithione, etc.
Hepatoprotective Drugs Promoting Energy Metabolism	Water-soluble vitamins (such as vitamin C, vitamin B complex), coenzyme A, coenzyme Q10, inosine, ornithine aspartate, alprostadil, etc.
Chinese Herbal Medicines and Extracts	Glycyrrhizin acid preparations, silymarin, oxymatrine, etc.

The above drug list is for reference only, and investigators can make their own judgments according to the actual situation.

APPENDIX 2: Chemical Drugs, Traditional Chinese Medicines or Dietary Supplements for Weight Loss

Non-hyperglycemic weight loss drugs, health care products and foods commonly used in clinical practices include but are not limited to the following:

Type	**Drug Name**
Lipase Inhibitors	Orlistat, etc.
Amylase Inhibitors	White kidney bean extract, etc.
Appetite Suppressants	Fenfluramine, sibutramine, etc.
Chinese Herbal Medicines	Lipid-lowering weight loss tablets, light-weight weight loss tablets, lipid-lowering weight loss capsules, etc.

The above drug list is for reference only, and investigators can make their own judgments according to the actual situation.

APPENDIX 3: List of Bacteria Used in Food

According to the List of Bacteria Used in Food promulgated by the Ministry of Health P.R.China, bacteria that may meet the definition of "probiotics" are mainly from *Lactobacillus* and *Bifidobacterium*, and may also be *Bacillus*, *Enterococcus*, *Streptococcus*, *Pediococcus*, *Leuconostoc*, *Clostridium butyricum*, *Actinomycetes* and *Saccharomyces*, etc. The list below is for reference only, and investigators can make their own judgments based on the actual situation.

	Name in Latin
I	*Bifidobacterium*
1	*Bifidobacterium adolescentis*
2	*Bifidobacterium animalis* （*Bifidobacterium lactis*）
3	*Bifidobacterium bifidum*
4	*Bifidobacterium breve*
5	*Bifidobacterium infantis*
6	*Bifidobacterium longum*
II	*Lactobacillus*
1	*Lactobacillus acidophilus*
2	*Lactobacillus casei*
3	*Lactobacillus crispatus*
4	*Lactobacillus delbrueckii* subsp. *Bulgaricus* （*Lactobacillus bulgaricus*）
5	*Lactobacillus delbrueckii* subsp. *lactis*
6	*Lactobacillus fermentium*
7	*Lactobacillus gasseri*
8	*Lactobacillus helveticus*
9	*Lactobacillus johnsonii*
10	*Lactobacillus paracasei*
11	*Lactobacillus plantarum*
12	*Lactobacillus reuteri*
13	*Lactobacillus rhamnosus*
14	*Lactobacillus salivarius*
III	*Streptococcus*
1	*Streptococcus thermophilus*

APPENDIX 4: Lipid-Controlling Drugs

Lipid-controlling drugs commonly used in clinical practices include but are not limited to the following:

	Type	**Drug Name**
Cholesterol Lowering Drugs	Statins	Lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin and pitavastatin, xuezhikang capsules, etc.
	Cholesterol absorption inhibitors	Ezetimibe
	Probucol	
	Bile acid sequestrants	Cholestyramine, colesevelam
	Other lipid-lowering drugs	Zhibitai capsules, policosanol
TG Lowering Drugs	Fibrates	Fenofibrate tablets, micronized fenofibrate, gemfibrozil, bezafibrate
	Niacin	Niacin (vitamin B3)
	High-purity fish oil drug products	
Novel Lipid-lowering Drugs	Microsomal TG transfer protein inhibitors	Lomitapide
	Apolipoprotein B_{100} synthesis inhibitors	Mipomersen
	Proprotein convertase subtilisin 9\kexin9 inhibitors	Evolocumab, alirocumab

The above drug list is for reference only, and investigators can make their own judgments according to the actual situation.

APPENDIX 5: Calculation Formula

Calculation Formula for Glomerular Filtration Rate (GFR)

GFR is calculated using the CKD-EPI formula:

Serum creatinine unit conversion: 1 mg/dL = 88.4 μmol/L

Gender	**Scr Range**	**EPI-GFR Formula, unit: $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$**
Female	Scr ⩽ 0.7mg/dL	$EPI\text{-}GFR=144\times[Scr(mg/dL)/0.7)]^{-0.329}\times0.993^{age}$
	Scr > 0.7mg/dL	$EPI\text{-}GFR=144\times[Scr(mg/dL)/0.7)]^{-1.209}\times0.993^{age}$
Male	Scr ⩽ 0.9mg/dL	$EPI\text{-}GFR=141\times[Scr(mg/dL)/0.9)]^{-0.411}\times0.993^{age}$
	Scr > 0.9mg/dL	$EPI\text{-}GFR=141\times[Scr(mg/dL)/0.9)]^{-1.209}\times0.993^{age}$

QTcF Calculation Formula

$QTcF = QT/RR^{0.33}$ (RR is the normalized heart rate)

APPENDIX 6: Birth Control, Definition of Female Subjects of Childbearing Age, and Contraception Requirements

➢ Definition of Female Subjects of Childbearing Age

Female subjects of non-childbearing age are defined as postmenopausal female subjects and premenopausal female subjects who had undergone sterilization. Postmenopause is defined as the absence of menstrual periods for ⩾12 consecutive months without alternative medical measures. FSH >40 MlU/mL can be determined as menopause by follicle-stimulating hormone (FSH) test in uncertain subjects. Sterilization procedures include bilateral tubal ligation or bilateral oophorectomy or hysterectomy.

Female subjects of childbearing age are defined as women who are anatomically and physiologically able to get pregnant without sterilization from menarche to menopause.

➢ Contraception Requirements

Female subjects of childbearing age must be negative in the pregnancy test at the screening phase;

During the screening phase to the last dose, female subjects of childbearing age and male subjects must also agree to one of the following operations:

- Complete abstinence of sex activities. Periodic abstinence (e.g., calendar, ovulation, symptom-temperature, postovulation method) is not permitted.
- One of the contraceptive methods with <1% correct failure rate:
  - — Intrauterine device (IUD) or intrauterine hormone-releasing systems with an annual failure rate < 1%
  - — Vasectomy for male subjects;
  - — Double-barrier method of contraception: condom and/or occlusive cap (diaphragm or cervical cap/dome cap), a barrier method with spermicide (foam/gel/film/cream/suppository) must be used as a supplementary measure.

The following contraception methods can be accepted within 3 months after the last dose:

- Rational use of combined (estrogen and progestin-containing) oral/injectable/transdermal hormonal contraceptives that inhibit ovulation;
- Rational use of oral/injectable/transdermal hormonal contraceptives that only contain estrogen and progestin and inhibit ovulation.

APPENDIX 7: Clinical Laboratory Tests

Item	Description
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count, neutrophil count, basophil count, eosinophil count, monocyte count, lymphocyte count, platelet count
Urinalysis	Urine pH, urine specific gravity, urine protein, urine glucose, urine red blood cells/urine occult blood, urine leukocytes, ketone bodies
Blood Biochemistry	Liver functions, including total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, albumin, total protein, lactate dehydrogenase; Renal function, including blood urea nitrogen or urea, creatinine, uric acid; Electrolytes, including sodium, potassium, chloride, calcium; blood lipids, including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides.
Coagulation Tests	Prothrombin time, international normalized ratio, activated partial thromboplastin time, thrombin time, and fibrinogen;
Thyroid Function Tests	Free tri-iodothyronine, free thyroxine and thyroid stimulating hormone.

Clinical laboratory tests are performed in the laboratories of each study site.

APPENDIX 8: Blood Sample Collection Schedule

Blood Sample Collection Schedule for Efficacy Endpoints

Index	Sampling Point	Sampling Deviation Time Window
V3		
➢ Fasting Blood Glucose ➢ Fasting HbA1c	0 h before breakfast on Day -7 to Day -5	Within 1 hour before meal
V4		
➢ Fasting Blood Glucose ➢ Fasting Insulin ➢ Fasting C-peptide ➢ Fasting LDL-C, HDL-C, TG, TC ➢ Fasting AST, ALT, GGT, TBIL ➢ Fasting C-reactive Protein ➢ Fasting Intestinal Flora Metabolomics Serum Samples	0 h before breakfast (standard meal) at Week 1 (Day 1)	Within 1 hour before meal
➢ Postprandial Blood Glucose ➢ Postprandial Insulin ➢ Postprandial C-peptide	0.5 hours after starting meal at Week 1 (Day 1)	±2 minutes
➢ Feces (if any)		From the day before the visit to the day of the visit
V5		
➢ Fasting Blood Glucose ➢ Fasting Insulin ➢ Fasting C-peptide ➢ Fasting LDL-C, HDL-C, TG, TC ➢ Fasting AST, ALT, GGT, TBIL	0 h before breakfast at Week 4 (Day 28)	Within 1 hour before meal
V6		
➢ Fasting Blood Glucose ➢ Fasting Insulin ➢ Fasting C-peptide ➢ Fasting HbA1c ➢ Fasting LDL-C, HDL-C, TG, TC ➢ Fasting AST, ALT, GGT, TBIL ➢ Fasting Intestinal Flora Metabolomics Serum Samples	0 h before breakfast (standard meal) at Week 8 (Day 56)	Within 1 hour before meal
➢ Postprandial Blood Glucose ➢ Postprandial Insulin ➢ Postprandial C-peptide	0.5 hours after starting meal at Week 8 (Day 56)	±2 minutes
➢ Feces (if any)		From the day before the visit to the day of the visit
V7		

Index	Sampling Point	Sampling Deviation Time Window
➢ Fasting Blood Glucose ➢ Fasting Insulin ➢ Fasting C-peptide ➢ Fasting HbA1c ➢ Fasting LDL-C, HDL-C, TG, TC ➢ Fasting AST, ALT, GGT, TBIL ➢ Fasting C-reactive Protein ➢ Fasting Intestinal Flora Metabolomics Serum Samples	0 h before breakfast (standard meal) at Week 12 (Day 84)	Within 1 hour before meal
➢ Postprandial Blood Glucose ➢ Postprandial Insulin ➢ Postprandial C-peptide	0.5 hours after starting meal at Week 12 (Day 84)	±2 minutes
➢ Feces (if any)		From the day before the visit to the day of the visit

PPK Blood Sample Collection Schedule

Sampling Point	Sampling Deviation Time Window
V4	Fasting in the morning
Before Breakfast On The Same Day (before the first dose) of V5-V7	Within 1 hour prior to dosing

The collection and treatment of blood samples are determined by the central laboratory. For details, please refer to the SOP of the central laboratory (see the *Laboratory Operation Manual*).

APPENDIX 9: Standard Meal Process

The meals used in all visits in this study refer to the "standard meal instant noodles (noodle weigh about 85 g)" uniformly provided by the Sponsor.

Subjects should avoid strenuous physical activity and high-calorie food intake in the night before the standard meal visit. On the day of the visit, the subjects should be fasting (have dinner not more than 22:00 on the day before the visit; or have the last food intake at least 8 hours before the visit; the subjects are allowed to drink water in the night).

1) In V4: The time starts from the first bite of "standard meal instant noodles", which is 0:00, and the intake is completed within the next 15 minutes. At 0.5 hours (allow ± 2 minutes) after starting to eat (0:00), blood samples are collected (refer to the *Laboratory Operation Manual* for sample treatment).

2) In V6 and V7: The time starts from the first bite of "standard meal instant noodles", which is 0:00, and the intake is completed within the next 15 minutes. After the first bite of the "standard meal instant noodles", the subjects should be administered with the investigational drug with about 200 mL warm water, and continue to eat immediately after taking the drug. At 0.5 hours (allow ± 2 minutes) after starting to eat (0:00), blood samples are collected (refer to the *Laboratory Operation Manual* for sample treatment). The subjects should keep having no other food and water, and do not do strenuous exercise until the completion of blood sample collection.

Method for taking the standard meal instant noodles:

(1) Flavoring: Take out the flavoring bag and pour the powder into the noodle bowl (without the oil bag);

(2) Soaking: add about 550 mL boiling water (it is recommended to be used immediately after boiling) to the instant noodle bowl (to the mark), cover the cap, and then start timing;

(3) Stirring: when the instant noodles have been immersed for 2-2.5 minutes, open the cap, stir the noodles, and then cover the cap;

(4) Preparing to eat: when the instant noodles have been immersed for 5-10 minutes, stir the noodles with chopsticks;

(5) Eating noodles: eat the noodles within 15 minutes, including all broken noodles as much as possible. The noodle soup can be taken fully or left according to personal preference.

APPENDIX 10: Self-Monitoring of Blood Glucose (SMBG) Procedures

In this study, all subjects are provided with blood glucose meters of the same brand and model and unified blood glucose test strips, and are instructed in the SMBG operation and precautions and reminded to record the test results in the subject diary in time as required. During the study, if any problem with the subject's operation or recording is found, repeated or targeted training should be given in time to improve the compliance of the operation.

During this study, subjects should undergo SMBG test under the guidance of the investigator. In case of poor blood glucose control, blood glucose monitoring at corresponding time points can be increased according to the guidance of the investigator. If there are suspected symptoms of hypoglycemia, the blood glucose should be measured as soon as possible.

During the introduction period and the entire study treatment phase (V4-V7), the investigator should inform the subjects to contact the study site if the fingertip blood glucose meets the following criteria in order to provide safety guidance to the subjects and timely assess the withdrawal criteria:

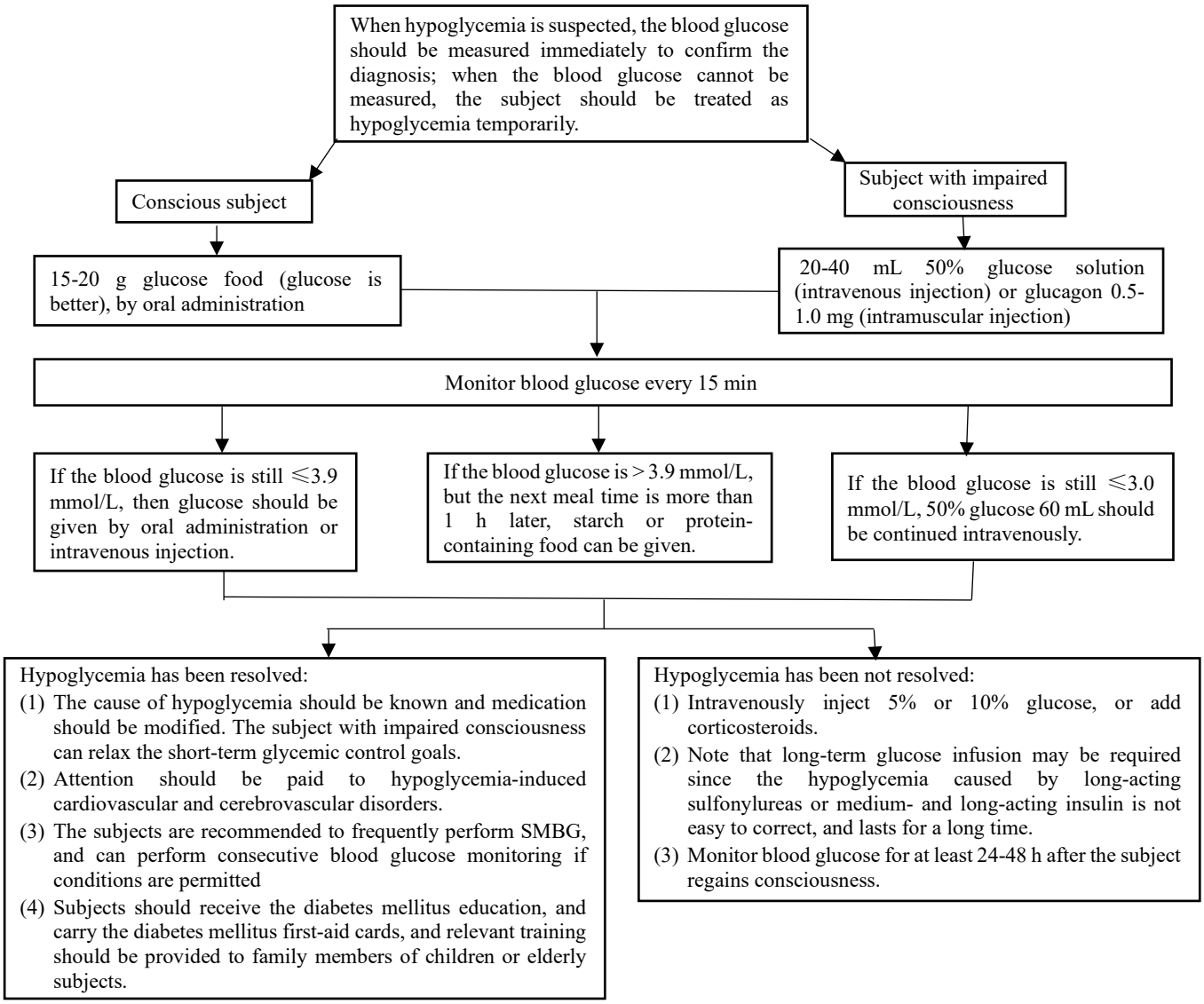
Hypoglycemia: at any time point during the treatment, the fingertip blood glucose is $\leqslant$3.9 mmol/L.

Hyperglycemia: first 6 weeks of the treatment phase (including Week 6), the fasting fingertip blood glucose is $\geqslant$15.0 mmol/L;

Week 7-12 of the treatment phase: the fasting fingertip blood glucose is $\geqslant$13.3 mmol/L.

The blood glucose value measured by the subject should be recorded in the subject diary in time. At each visit, including the follow-up visit, subjects should bring a blood glucose meter and diary for review by the investigator.

APPENDIX 11: First Aid Measures for Hypoglycemia (Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition))



For the conscious subject

The subject should take 15-20 g glucose food (glucose is preferred) orally, and then measured the blood glucose every 15 minutes. When the blood glucose is ⩽3.9 mmol/L, the subject should be given glucose by oral administration or intravenous injection; when the blood glucose is higher than 3.9 mmol/L, but the next meal is more than 1 hour later, starch or protein-containing food can be given; when the blood glucose is still ⩽3.0 mmol/L, then the subject should be intravenously injected with 60 mL 50% glucose solution.

For the subject with impaired consciousness

The subject should be given 20-40 mL 50% glucose solution by intravenous injection, or 0.5-1.0 mg glucagon by intramuscular injection, and then measured the blood glucose every 15 minutes. When the blood glucose is ⩽3.9 mmol/L, the subject should be given glucose by oral administration or intravenous injection; when the blood glucose is higher than 3.9 mmol/L, but the next meal is more than 1 hour later, starch or protein-containing food can be given; when the blood glucose is still ⩽3.0 mmol/L, then the subject should be intravenously injected with 60 mL 50% glucose solution.

If the hypoglycemia has been not resolved:

1) Intravenously inject 5% or 10% glucose, or add corticosteroids.
2) Monitor blood glucose for at least 24-48 hours after the subject regains consciousness.

APPENDIX 12: Recommendations for Diet and Exercise Treatment (Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020))

Medical nutrition therapy for Type 2 Diabetes Mellitus (T2DM)

Medical nutrition therapy is a basic treatment of special intervention measures for the nutrition problems of patients with diabetes mellitus or prediabetes mellitus, including individualized nutritional assessment, nutritional diagnosis, establishment of corresponding nutritional intervention plans, and implementation and monitoring within a certain period. This therapy can help maintain ideal body weight and prevent malnutrition by changing dietary patterns and habits, adjusting nutritional structure, and assisting blood glucose control, and is an essential part of the prevention, treatment, self-management and education of diabetes mellitus and its complications.

I. Objectives of medical nutrition therapy

The objectives of medical nutrition therapy are determined according to the requirements of domestic and foreign health industry standards and guidelines:

1. To promote and maintain healthy eating habits, emphasize appropriate food selection, and improve overall health condition.
2. To achieve and maintain reasonable body weight, obtain good control of blood glucose, blood pressure, and blood lipids, and delay the occurrence of diabetic complications.
3. To provide a nutritionally balanced meal. More types of nutrient-dense food can be selected to meet demands of individual background, cultural, etc., and behavioral changes can be made.

II. Dietary nutritional factors

(I) Energy

1. Patients with prediabetes mellitus or diabetes mellitus should receive the individualized energy balance program to achieve or maintain the ideal body weight and meet the nutritional requirements in different situations.
2. All overweight or obese diabetic patients should modify the lifestyle and control the total energy intake to lose at least 5% of body weight.
3. It is recommended that the energy intake of diabetic patients refer to the general coefficient method, and the energy intake is calculated according to 105-126 kJ (25-30 kcal)·kg^{-1} (standard body weight)·d^{-1}. Then the coefficients are adjusted according to the patient's body height, body weight, gender, age, activity level, stress situation, etc. Long-term nutritional therapy with very low energy (<800 kcal/d) is not recommended for T2DM patients.

(II) Fat

1. Different types of fat have different effects on blood glucose and cardiovascular disorders, so it is difficult to accurately recommend the energy supply of dietary fat. It is generally believed that the energy provided by dietary fat should account for 20%-30% of the total energy. In the case of high-quality fats (such as fats composed of monounsaturated fatty acids and n-3 polyunsaturated fatty acids), the fat-to-energy ratio can be increased to 35%.
2. The intake of saturated and trans fatty acids should be limited as much as possible. Monounsaturated fatty acids and n-3 polyunsaturated fatty acids (such as fish oil, some nuts and seeds) help improve blood glucose and blood lipids, and can be appropriately increased.
3. With reference to the Chinese Dietary Guidelines (2016), excessive intake of dietary cholesterol should be controlled.

(III) Carbohydrate

1. The results of the Atherosclerosis Risk in Community (ARIC) study showed that there is minimum risk of all-cause mortality when carbohydrates provide 50%-55% of total energy. Considering the dietary habits of diabetic patients in China, it is suggested that the energy provided by carbohydrates in the diet of most diabetic patients accounts for 50%-65% of the total energy. The diabetic patients with poor postprandial blood glucose control should appropriately decrease the carbohydrate-to-energy ratio. Long-term use of very low carbohydrate diets is not recommended.
2. While controlling the total amount of carbohydrates, low-glycemic index carbohydrates should be selected, non-starchy vegetables, fruits, and whole grains can be appropriately increased, and the intake of refined grains can be decreased. Whole grains should account for more than half of the total grains. Whole grain intake is inversely associated with risk of all-cause mortality, coronary heart disease, T2DM, and colorectal cancer.
3. Meals should be timed and rationed. Insulin-injected patients should maintain carbohydrate intake to match insulin dose and onset of effect.
4. The dietary fiber intake should be increased. The daily dietary fiber intake for adults should be >14 g/1,000 kcal. The daily dietary is inversely associated with risk of all-cause mortality, coronary heart disease, T2DM, and colorectal cancer.
5. The intake of sucrose and fructose products (such as corn syrup) should be controlled strictly.
6. Diabetic patients who like sweets can properly consume glucose alcohols and non-nutritive sweeteners.

(IV) Protein

1. For diabetic patients with normal renal function, the protein intake can account for 15%-20% of the protein-to-energy ratio to ensure more than half of the high-quality protein.
2. Protein intake in diabetic patients with overt proteinuria or decreased glomerular filtration rate should be controlled at 0.8 g/kg body weight per day.

(V) Alcohol consumption

1. Alcohol consumption is not recommended for diabetic patients. If the patients drink alcohol, the total energy contained in the alcohol should be calculated.
2. The alcohol consumption should be not more than 15 g/day for females and not more than 25 g/day for males (15 g alcohol is equivalent to 350 mL beer, 150 mL wine or 45mL distilled spirits). Drink not more than twice a week.
3. Alcohol-induced hypoglycemia should be vigilant, especially in patients taking sulfonylureas or injecting insulin and insulin analogs who should avoid drinking under the fasting condition and strictly monitor blood glucose.

(VI) Salt

1. Salt intake should be limited to less than 5 g/day, and may be further limited for diabetic patients with hypertension.
2. In addition, the intake of high-salt foods, such as monosodium glutamate, soy sauce, salt-soaked and other processed foods, seasoning sauces should be limited.

(VII) Micronutrients

Diabetic patients are prone to be deficient in B vitamins, vitamin C, vitamin D, and many micronutrients such as chromium, zinc, selenium, magnesium, ferrum, and manganese, which can be supplemented appropriately according to the results of nutritional evaluation. Diabetic patients with long-term use of metformin should prevent vitamin B12 deficiency. It is not recommended to supplement a large amount of vitamin E, vitamin C, carotene and other drug product with antioxidant effects for a long term since their long-term safety remains to be verified.

III. Nutrition Education and Management

Nutrition education and management can help improve glucose tolerance, reduce the risk of developing diabetes mellitus, and help reduce the occurrence of chronic complications in diabetic patients. Individualized objectives and plans for education and management of diabetic patients should be established, and together with exercise and smoking cessation, should be regarded as the basis for the prevention and treatment of diabetes mellitus and its complications.

Exercise Therapy for T2DM

Exercise plays an important role in the comprehensive management of T2DM patients. Regular exercise can increase insulin sensitivity, improve body composition and quality of life, help to control blood glucose, reduce cardiovascular risk factors, and have a significant primary prevention effect on people at high risk of diabetes mellitus. Epidemiological studies have shown that regular exercise for more than 8 weeks can decrease HbA1c in T2DM patients by 0.66%; persistent regular exercise can significantly decrease the risk of death in diabetic patients.

T2DM patients should comply with the following principles at exercise:

1. Exercise therapy should be carried out under the guidance of a physician. Necessary health evaluation and exercise ability assessment before exercise will help to ensure the safety and scientificity of exercise therapy.
2. Adult T2DM patients should take the moderate-intensity (50%-70% of the maximum heart rate, a little hard during exercise, and rapid heartbeat and breathing but not hurried) aerobic exercise for at least 150 minutes per week (e.g., exercise for 5 days per week, 30 minutes each time). Even a short-term physical exercise (such as 10 minutes) for a total of 30 minutes/day is beneficial.
3. Moderate-intensity physical exercise include: brisk walking, tai chi, cycling, table tennis, badminton, golf, etc. High-intensity physical exercise include fast-paced dancing, aerobics, swimming, cycling uphill, football, basketball, etc.
4. If there are no contraindications, it is best to take resistance exercise 2-3 times a week (with an interval of $\geqslant$ 48 hours) to exercise muscle strength and endurance. The exercise parts should include major muscle groups, such as upper limbs, lower limbs, and trunk, at the training intensity of moderate. A combination with resistance and aerobic exercises can gain greater metabolic improvement.

5. The establishment of exercise prescription should follow the individualization principle. Exercise items should be adapted to the subject's age, condition, preferences, and physical tolerance, and regular assessments should be given to adjust exercise plans in a timely manner. The use of physical exercise wearables, such as pedometers, can help improve exercise compliance. Blood glucose monitoring should be strengthened before and after exercise, and subjects should be advised to temporarily adjust their diet and drug treatment plans to avoid hypoglycemia during heavy or intense exercise. Attention should be paid to replenish water in time during exercise.
6. Patients should develop healthy habits. Development of active lifestyles such as increasing daily physical activity, breaking sedentary behaviors, and reducing sedentary time may help incorporate beneficial physical exercise into daily life.
7. Exercise should be contraindicated in case of severe hypoglycemia, acute metabolic complications such as diabetic ketoacidosis, concomitant acute infection, proliferative retinopathy, severe cardiovascular and cerebrovascular disorders (unstable angina pectoris, severe arrhythmia, transient ischemic attack), etc., and can be resumed gradually after the condition is controlled and stabilized.
8. T2DM patients generally do not need to delay exercise due to hyperglycemia as long as they feel well. Caution should be given to ensure water replenishing at exercise if the blood glucose is >16.7 mmol/L during strenuous physical activity.

Smoking Cessation

Smoking is harmful to health. Smoking is not only a major risk factor for cancer, respiratory and cardiovascular and cerebrovascular disorders, but also closely related to the occurrence and development of diabetes mellitus and its complications.

Diabetic subjects often have symptoms of easy hunger. After smoking cessation, the appetite-suppressing effect of nicotine is relieved, and increased eating can cause weight gain. Smoking cessation also alters the intestinal flora and may also lead to weight gain. However, the adverse effects of weight gain cannot offset the beneficial effects of smoking cessation. Therefore, physicians should encourage patients to quit smoking and focus on weight management during smoking cessation. Smoking cessation measures include behavioral and drug interventions.

Behavioral interventions include:

1. Routine education should be given to diabetic patients to inform them of the dangers of smoking, its adverse effects on diabetes mellitus, the benefits of smoking cessation, and smoking cessation measures.
2. Short-term counselling and smoking cessation hotlines are available to patients.
3. Patients should be assessed for the smoking status and nicotine dependence to formulate corresponding smoking cessation objectives.
4. Psychological and behavioral support should be provided for patients, including seeking group support from family members and friends or other patients, individualized diet and exercise treatment plans and smoking cessation plans should be formulated for patients, and regular follow-up visits should be given.
5. Patients who have quit smoking successfully will receive follow-up visits for 6-12 months (such as telephone calls) to help prevent relapse.

Nicotine replacement therapy, bupropion, varenicline and other drugs can be used in the drug intervention to help patients to quit smoking. These drugs can increase the success rate of smoking

cessation and can be used under the guidance of smoking cessation experts. In addition, these drug interventions may delay weight gain after smoking cessation. Therefore, ex-smokers can focus on smoking cessation first and then on weight management. In addition, the use of metformin, sodium-glucose cotransporter-2 inhibitor (SGLT2i), glucagon-like peptide-1 receptor agonist (GLP-1RA) and other hypoglycemic drugs that help reduce weight can help prevent weight gain after smoking cessation while treating diabetes mellitus. Compared with minimal intervention or usual care, a combination of drug and behavioral interventions can increase the success rates of smoking cessation to 70%-100%.