Protocol Synopsis

Study Title	A Single-center, Randomized, Double-blind, Multiple Ascending Dose, Placebo-controlled Phase Ib/IIa Clinical Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Early Pharmacodynamics of BGT-002 Tablets in Subjects with NASH
Objectives	➢ **Primary Objective:** To evaluate the safety and tolerability of BGT-002 Tablets in subjects with NASH after oral administration; ➢ **Secondary Objectives:** 1) To evaluate the pharmacokinetics (PK) of BGT-002 Tablets in subjects with NASH after oral administration; 2) To evaluate the effect of BGT-002 on lipid metabolism in subjects with NASH; 3) To evaluate the effect of BGT-002 on biochemical indicators related to liver function in subjects with NASH. ➢ **Exploratory Objective:** To evaluate the biomarker profile of BGT-002 in subjects with NASH.
Protocol No.	BGT-002-004
Sponsor	Burgeon Therapeutics Co., Ltd.
Clinical Study Approval No.	2023LP00117/ 2023LP00118
Registration Category	Chemical Drug Class 1
Study Facility	The First Hospital of Jilin University
Phase of Development	Phase Ib/IIa
Investigational Products Drug and Storage Conditions	**Study Drug: BGT-002 Tablets** It was developed by Burgeon Therapeutics Co., Ltd. and manufactured by ApicHope Pharmaceutical Co., Ltd. Drug Batch No.: XXX Dosage Form: Tablet Strength: 50 mg/tablet; Mode of Administration: Oral under fasting conditions Shelf Life: MM/YYYY Storage Condition: Sealed, stored in a dry place below 25°C **Control Drug: BGT-002 Placebo** It was developed by Burgeon Therapeutics Co., Ltd. and manufactured by ApicHope

	Pharmaceutical Co., Ltd. Drug Batch No.: XXX Dosage Form: Tablet Strength: 50 mg/tablet; Mode of Administration: Oral under fasting conditions Shelf Life: MM/YYYY Storage Condition: Sealed, stored in a dry place below 25°C The batch number and shelf life of the above study drug and control drug shall be subject to the packaging.
Key Information of Preclinical Study	**Pharmacodynamic Study:** The results of *in vitro* pharmacodynamic studies showed that the coenzyme A derivative of BGT-002 (ZM326E-CoA) could notably decrease the catalytic activity of ACLY with an IC_{50} of 5.31 ± 1.21 μM. BGT-002 could strongly inhibit the *de novo* synthesis of triglyceride (IC_{50}: 0.76 ± 0.20 μM) and cholesterol (IC_{50}: 1.82 ± 1.89 μM) from sodium [1,2-^{14}C]-acetate in mouse primary hepatocytes in a significant dose-dependent manner. Similarly, using [^{14}C]-citrate as a substrate, BGT-002 could significantly inhibit the *de novo* synthesis of triglyceride (IC_{50}: 13.26 ± 1.89 μM) and cholesterol (IC_{50}: 5.53 ± 2.49 μM) in mouse primary hepatocytes in a significant dose-dependent manner. The inhibition of BGT-002 on lipid synthesis could be partially reversed by Triacsin C (a long-chain acyl-CoA synthetase indicator), indicating its active form, ZM326E-CoA, is necessary for ACLY inhibition. Moreover, BGT-002 could effectively enhance fatty acid β-oxidation in mouse primary hepatocytes, performing comparably to the commercially available drug ETC-1002 (bempedoic acid). In the *in vivo* pharmacodynamic studies, it was found that long-term administration of BGT-002 significantly reduced hyperlipidemia induced by a high-fat, high-glucose, and high-cholesterol diet and hepatic lipid accumulation in NAFLD model (C57BL/6J mice) and NASH model (*ob/ob* mice). Besides, it significantly reduced the degree of liver function damage caused by dietary stress (ALT and AST significantly reduced). Immunohistochemical staining results showed that long-term administration of BGT-002 reduced inflammatory cell infiltration; picrosirius red staining results indicated a significantly reduced liver fibrosis compared to the model control group. The levels of NASH-related plasma biomarkers such as FGF21 and TIMP-1 were significantly decreased after long-term administration of BGT-002. We also saw that long-term administration of BGT-002 could significantly ameliorate hepatic lipid accumulation, inflammation, and fibrosis in the HFD-MCD diet-induced NASH model (C57BL/6J mice). The anti-fibrotic pharmacodynamics of BGT-002 was evaluated in a CCl_4-induced mouse model of liver fibrosis. It was found that long-term administration of BGT-002 significantly reduced collagen deposition, and the pathological score also showed that long-term administration of BGT-002 significantly reduced CCl_4-induced fibrosis. More importantly, we performed

	pharmacodynamic evaluations for over 130 days on a non-human primate (cynomolgus monkey) model for NASH that closely resembled human NASH onset characteristics. The study results showed that long-term administration of BGT-002 had pharmacological effects to significantly improve NASH and reverse fibrosis, with a significant increase in the content of ketone bodies represented by β-hydroxybutyrate in serum and a significant decrease in the hepatic inflammatory marker (hs-CRP), showing good tolerability. This result demonstrates the favorable safety profile of BGT-002 in addition to its significant efficacy. Therefore, BGT-002 has the pharmacological effects of significantly inhibiting de novo lipid synthesis in the liver (cells), promoting fatty acid oxidation, significantly improving NASH, and reversing hepatic fibrosis. This result demonstrates the favorable safety profile of BGT-002 in addition to its significant efficacy. The secondary pharmacodynamic and safety pharmacology study data also demonstrate that BGT-002 has good target selectivity and safety. **Pharmacokinetic Study:** BGT-002 had good pharmacokinetic profiles in mice and dogs, with an absolute bioavailability of 92.7% and 53.8% by gavage or oral administration, respectively. BGT-002 was rapidly absorbed in mice, with the time to maximum plasma concentration (T_{max}) of 0.083–0.5 h and the plasma elimination half-life ($t1_{/2}$) of 1.89–8.07 h. The high exposure of BGT-002 in plasma and liver was favorable for its efficacy. The major metabolite of BGT-002 in hepatocytes from various species was the glucuronide conjugate M2, with significantly higher levels produced in human, monkey, and dog hepatocytes compared to those in rats and mice. BGT-002 was mainly catalyzed by UGT2B7 to generate glucuronide conjugate M2. Within the tested concentration range (0.10–100 μM), BGT-002 had no time-dependent inhibition on major CYP450 enzymes and did not induce CYP1A2, CYP2B6, or CYP3A4. BGT-002 was highly permeable and efflux transporters in Caco-2 cells were not involved in its transportation. **Toxicology Study:** Safety pharmacology (ICR mice, Beagle dogs), single-dose toxicity (ICR mice, Beagle dogs), repeated-dose toxicity (ICR mice, Beagle dogs), and genotoxicity results all suggest that BGT-002 has a good safety profile. The specific findings are as follows: (1)Within the observation range of pre-dose and 24 h post-dose in ICR mice, no significant abnormality was observed in various test indicators related to involuntary movement, autonomic nervous system, sensorimotor system, neuromuscular system and behavior in BGT-002 30 mg/kg, 100 mg/kg and 300 mg/kg groups; (2)Beagle dogs were administered with BGT-002 by single oral gavage and monitored continuously for 24 h post-dose. No drug-related effects on cardiovascular and respiratory systems were observed in the BGT-002 10 mg/kg, 30 mg/kg, and 100 mg/kg groups compared with the vehicle control group and baseline measurements before administration; (3)The maximum tolerated dose (MTD) of BGT-002 was 1000 mg/kg following single

	doses at 100, 300, and 1000 mg/kg by oral gavage in ICR mice; (4)The maximum tolerated dose (MTD) of BGT-002 was 600 mg/kg following single doses at 30, 200, and 600 mg/kg by oral gavage in Beagle dogs; (5)The no observed adverse effect level (NOAEL) of BGT-002 was 30 mg/kg after oral gavage (30, 100, and 300 mg/kg) once daily for 28 consecutive days in ICR mice; (6)The no observed adverse effect level (NOAEL) of BGT-002 was 360 mg/kg after oral gavage (30, 100, and 360 mg/kg) once daily for 28 consecutive days in Beagle dogs; (7)BGT-002 did not induce reverse mutation in Salmonella typhimurium strains TA97, TA98, TA100, TA102 and TA1535; (8)No increase in the chromosomal structural aberration rate of CHL cells induced by BGT-002 was observed after 4 h and 24 h treatment under -S9 conditions, and the result was negative. Although the chromosomal aberration rate of BGT-002 in the 50 μg/mL dose group was 6.67% (within 5%–10%) after 4 h treatment under + S9 conditions, which was a suspicious positive result, BGT-002 did not induce an increase in the micronucleus rate of bone marrow erythrocytes in KM mice at ≤ 1000 mg/(kg/d), confirming that BGT-002 has no teratogenic toxicity. The result of the comet assay in SD rats also showed that BGT-002 did not induce DNA damage in liver and gastric cells at doses ≤ 600 mg/(kg/d). In addition, during the long-term pharmacodynamic evaluation, no significant abnormalities in body weight, food intake, and other vital signs were observed in mouse models (ApoE-/- mice for 24 weeks, ob/ob mice for 9 weeks, C57BL/6J mice for up to 19 weeks) and cynomolgus monkey models (at a dose of 20 mg/kg), and no drug-related abnormal clinical observations were observed. In terms of drug exposure, the plasma C_{max} was 148.7 μg/mL after 12 weeks of high dose administration (50 mg/kg) in ApoE-/- mice, 93.3 μg/mL after 6 weeks of high dose administration (60 mg/kg) in ob/ob mice, and 134.05 μg/mL after 1 week of administration (20 mg/kg) in cynomolgus monkeys. In the completed long-term toxicity study in mice, C_{max} was 62.7 μg/mL at 30 mg/kg; 210 μg/mL at 100 mg/kg, and 349 μg/mL at 300 mg/kg 28 days post-dose. In the completed long-term toxicity study in Beagle dogs, C_{max} was 199 μg/mL at 30 mg/kg; 382 μg/mL at 100 mg/kg, and 570 μg/mL at 300 mg/kg 28 days post-dose. The liver function evaluation results obtained during the pharmacodynamic study found that the activities of ALT and AST in plasma did not increase significantly with the prolongation of administration. However, due to the improvement effect of long-term administration on NAFLD, liver function was significantly improved. The above study results also further suggest the safety of the study drug in long-term administration.
Key Information from Previous Trials	**Clinical Trials Conducted:** Till now, 3 single-center clinical trials have been carried out for BGT-002 tablets. The specific information is summarized as follows: **Main Information on Clinical Trials Conducted for BGT-002 Tablets**

Project No.	Phase	Population	Number of Subjects Enrolled (BGT-002 Tablets: Placebo)	Dosing Regimen and Design
BGT-002-001	Phase Ia-SAD	Healthy Subjects	59 (45:14)	12.5–300 mg, PO, single dose, randomized, double-blind
BGT-002-002	Phase Ia-MAD		36 (27:9)	25–75 mg/day, PO for 14 consecutive days, randomized, double-blind
BGT-002-003	Phase Ia-FE		14 (without placebo)	100 mg (D1, D15), PO, randomized, open-label, two-period, two-sequence, two-way crossover

Pharmacokinetics

Based on some available PK data, the exposure of BGT-002 in human plasma demonstrated a good dose dependency after administration of BGT-002 tablets.

As of January 04, 2023, the mean C_{max} after single doses of BGT-002 at 12.5 mg–300 mg in healthy subjects was 1.61 μg/mL–48.88 μg/mL, the AUC_{last} was 32.4 μg·h/mL–2703.12 μg·h/mL, the median T_{max} (25 mg–300 mg groups) occurred at 1.00 h–1.75 h, and the mean $T_{1/2}$ ranged from 25.0 h–75.1 h. The half-life at single doses in healthy subjects showed a tendency to increase with higher doses.

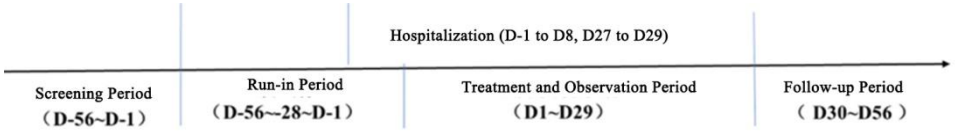
As of December 08, 2022, a total of 12 subjects (11 males and 1 female) were enrolled in the BGT-002 25 mg dose group of the multiple-dose trial for healthy subjects for 14 consecutive days. The C_{max} was 14.1 μg/mL and $AUC_{0\text{-}24h}$ was 257.1 μg·h/mL on Day 14 after multiple-dose administration; there were 12 subjects (10 males and 2 females) in the 50 mg dose group. After 14 days of continuous administration, the drug concentration was close to a steady state. On Day 14, after multiple-dose administration, the $C_{max,ss}$ was 27.1 μg/mL and $AUC_{0\text{-}24h,ss}$ was 513.9 μg·h/mL. The pharmacokinetics exhibited good linearity after continuous administration at 25 mg and 50 mg.

As of January 04, 2023, after administration with a high-fat meal in healthy subjects in the food effect trial, the median T_{max} was 3.50 h, C_{max} was 12.18 μg/mL, AUC_{last} was 571.31 μg·h/mL, and $t_{1/2}$ was 41.27 h; after administration under fasting conditions, the median T_{max} was 1.50 h, C_{max} was 16.64 μg/mL, AUC_{last} was 579.70 μg·h/mL and $t_{1/2}$ was 41.07 h. After administration following a high-fat meal, the T_{max} was delayed and the peak concentration decreased slightly, but the degree of drug absorption hardly changed.

Safety Results

No SAEs, life-threatening TEAEs, or TEAEs leading to death occurred during the Phase Ia single-dose clinical trial in healthy subjects. There were no TEAEs leading to premature withdrawal of any subject from the study or discontinuation of the study drug. A total of 58 subjects were enrolled in dose groups 1–8 (12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg), and a total of 24 (41.1%) subjects experienced 35

	TEAEs, including 31 drug-related AEs in 22 subjects. Apart from 1 case of white blood cell decreased and 1 case of upper respiratory infection, both in Grade 2, all others were in Grade 1. Common AEs possibly related to the drug included bradycardia sinus (N=13, 22.4%), shortened PR interval (N=4, 6.9%), and elevated AST (N=2, 3.4%). The incidence of bradycardia sinus and specific heart rate values in each group were as follows: For the 50 mg group: 37.5%, N = 3 (46 bpm, 46 bpm, and 44 bpm, respectively); 100 mg group: 37.5%, N = 3 (46 bpm, 46 bpm, and 44 bpm, respectively); 150 mg group: 12.5%, N = 1 (48 bpm); 200 mg group: 25%, N = 2 (43 bpm and 49 bpm); 250 mg group: 12.5%, N=1 (40 bpm); 300 mg group: 37.5%, N=3 (45 bpm, 44 bpm, and 47 bpm, respectively). The frequency and severity of bradycardia did not increase with increasing doses of BGT-002. The frequency and severity of the remaining TEAEs did not increase with increasing doses of BGT-002 and were not related to the dose level of BGT-002. During the Phase Ia multiple-dose clinical trial in healthy subjects, a total of 24 subjects were enrolled in 25 mg and 50 mg dose groups. After 2 weeks of administration, 15 subjects (62.5%) experienced 21 AEs, including 8 drug-related AEs occurred in 6 subjects (25%), all of which were in Grade 1; common drug-related AEs included diarrhea (N = 3, 12.5%), triglycerides increased (N = 3, 12.5%) and high-sensitivity C-reactive protein increased (N = 2, 8.3%). The frequency and severity of TEAEs did not increase with increasing doses of BGT-002 and were not related to the dose level of BGT-002. During the Phase Ia clinical trial on food effect in healthy subjects, a total of 14 subjects (13 males and 1 female) were enrolled, of which 6 subjects (42.9%) experienced 10 AEs, including 1 in Grade 3, 2 in Grade 2, and the rest in Grade 1. No serious adverse events occurred. A total of 5 drug-related AEs occurred in 4 subjects (28.1%), all of which were in Grade 1; drug-related AEs included urine white blood cell increased (N = 1, 7.1%), microscopic hematuria (N = 1, 7.1%), upper respiratory tract infection (N = 1, 7.1%), white blood cell count increased (N = 1, 7.1%), and blood neutrophil count increased (N = 1, 7.1%). **Phase Ib/IIa Starting and Effective Dose Estimation** The results of preclinical chronic toxicity studies showed that the NOAEL of BGT-002 was 30 mg/kg in mice and 360 mg/kg in Beagle dogs, which corresponded to human equivalent doses (HEDs) of 2.66 mg/kg and 209 mg/kg respectively. With a safety factor of 10, the maximum recommended starting doses (MRSDs) for humans were 16 mg and 1254 mg based on a body weight of 60 kg. Preclinical pharmacodynamic studies showed that the observed effective dose of BGT-002 in mice was < 15 mg/kg, which was 1.33 mg/kg after conversion to HED; the observed effective dose in rhesus monkeys was 20 mg/kg, which was 8 mg/kg after conversion to HED. Based on the analysis of preclinical pharmacodynamic data, it is found that the pharmacological effect of BGT-002 in improving NAFLD is not weaker than ETC-1002, while the clinical exposure of BGT-002 is about 2–3 times higher than that of ETC-1002.

	The dosage of ETC-1002 is 180 mg once a day. Therefore, we expect that the clinically effective dose of BGT-002 may be 60 mg–90 mg. **Pharmacodynamic Results** No data available up to now.
Study Design	**Overall Design** This study is a single-center, randomized, double-blind, multiple ascending doses (MAD), placebo-controlled phase Ib/IIa clinical trial of BGT-002 Tablets in subjects with NASH to evaluate the safety, tolerability, pharmacokinetics (PK) and early pharmacodynamics (PD) of BGT-002 Tablets. The number of subjects: A total of 48–60 subjects are planned to be enrolled in this study. **Study Flow** Study Schedule:  This study includes the screening period (D-56–D-1), run-in period (D-56–-28–D-1), treatment and observation period (D1–D29), and follow-up period (D30–D56). There will be a total of 8 return visits in the 50 mg and 75 mg groups: Visit 1-D-56–D-1 in the Screening Period, Visit 2-D-56–-28–D-1 in the Run-in Period, Visit 3-D-1 at the End of Run-in Period, Visits 4–8-D15, D22, D26, and D27 in the Treatment and Efficacy Observation Period. The Follow-up Period will be D56 ± 5 days and there will be 2 hospitalization periods: 9 days in D-1–D8 and 3 days in D27–D29. In addition to the above visits, return visits will be required for patients in the 100 mg, 150 mg, and 200 mg (alternative) groups on D31, D35, D38, and D41. During the study, if necessary, additional visits may be added according to the individual conditions of the subjects. After signing the informed consent form, subjects will enter the screening period (D-56–D-1) for preliminary eligibility evaluation. Subjects who pass the preliminary screening will enter a 4 to 8-week run-in period (D-56–-28–D-1), during which subjects will be required to maintain their previous living habits and diet structure. If subjects have received one body weight measurement and MRI-PDFF examination and have obtained the results before screening, they will be subject to another body weight measurement, MRI-PDFF examination, and other screening tests at an interval of 4–8 weeks from the first time. Subjects who meet the enrollment criteria will be admitted to the ward on D-1, receive randomization in this trial, and enter the treatment and observation period (D1–D29). During the treatment and observation period (D1–D28), subjects will be given BGT-002 tablets or a placebo according to the randomization number every morning under fasting conditions. After completing the corresponding visit, they can enter the follow-up period (D30–D56). All adverse events should be observed and recorded from post-administration to the end

of the trial, and appropriate treatment and handling measures should be adopted if necessary. In case of any abnormal indicator with clinical significance during the trial, the subjects should return to the hospital for re-examination as required by the investigator. After the investigator judges that the abnormal value becomes normal and the abnormality is not clinically significant or has become stable without the need for further tracking, they can be discharged.

Dose Group Design

It is originally planned to set 3-4 dose groups in this study, and the dose ascending design is as follows: 50 mg, 75 mg, 100 mg, and 125 mg (alternative). In this trial, it is planned to start with 50 mg as the lowest dose group. During the study, whether to continue to ascend to a higher dose group or adjust the dose ascending ratio will be determined based on available data.

As of September 13, 2023, based on the results of the completed interim analysis for three dose groups (50 mg, 75 mg and 100 mg), after discussion, the Sponsor and investigator decided to add 150 mg and 200 mg (alternative) groups for a 28-day continuous administration study, with 3 sentinels in the 150 mg and 200 mg (alternative) groups, respectively (2 subjects in the test group, and 1 subject in the placebo group) and observe for 8 days. If the safety is good, the remaining subjects will continue to be enrolled in this dose group (7 subjects in the test group and 2 subjects in the placebo group).

Dose (mg)	50	75	100	150	200 (Alternative)
Number of Subjects Study Drug + Placebo	9+3	9+3	9+3 (Male:female = close to 1:1)	9+3	9+3

Each dose group will randomly include 12 screened eligible subjects with NASH, with 9 taking the study drug orally and 3 taking the placebo orally. A total of 48-60 subjects will be included in the study. Whether to conduct the dose expansion study will be based on the results of the dose ascending stage.

- **Dose Ascending Principle:**
  1) In this trial, it is planned to start with 50 mg as the lowest dose and 200 mg as an alternative dose. A total of 4 to 5 dose groups will be selected from 50 mg, 75 mg, 100 mg, 150 mg, and 200 mg (alternative) groups, and the trial will be gradually carried out according to the above set doses.
  2) After the investigator and sponsor determine that 50% of subjects in each dose group have good results for 14-day safety evaluations, the trial can proceed to the next dose group. If necessary, subsequent trial protocols may be appropriately adjusted based on previous safety and PK analysis results (such as increasing or decreasing administration observation time or dose).
  3) If the criteria for termination of dose ascending are met during dose ascending, even if the predetermined maximum dose has not been reached, the dose ascending should be terminated.

	4) After the maximum estimated dose is reached by dose ascending, the investigator and the sponsor will discuss and analyze the existing safety and PK data before deciding whether to continue the next dose exploration. Any continuation will be subject to the approval of the Ethics Committee. ➢ **Stopping Criteria for Dose Ascending:** Within 14 days after the first dose, if any of the following criteria are met, the investigator and the sponsor will discuss and analyze the reasons and judge the impact on subsequent trials to decide whether to terminate dose ascending: 1)In the same dose group, more than 1/2 of subjects experience Grade 2 and above AEs related to the study drug; or more than 1/3 of subjects experience Grade 3 and above AEs related to the study drug; 2)The trial should be suspended if 1 case of serious adverse event (SAE) related to the study drug occurs during the trial; 3)Based on the available PK data, the investigator agrees with the sponsor that there is no need to continue the trial.
Dosing Regimen	In this trial, the drug will be orally administered under fasting conditions, once in the morning with warm water for 4 consecutive weeks. Subjects will be required to fast for at least 10 h pre-dose on D1 and D28 and 4 h post-dose on the days of intensive blood sampling (D1 and D28) (intolerant subjects can take food 30 min post-dose). For the rest of the time (D2–D27), subjects should try to fast for 30 min post-dose. Except for water deprivation 1 h pre-dose and 2 h post-dose on the days of intensive blood sampling (D1 and D28), subjects can have free access to water in the rest time (D2–D27). Subjects will be required to remain sitting and out-of-bed activities will be limited within 2 h post-dose on D1 and D28 (transient lying position can be kept during ECG examination). Normal indoor activities will be allowed for the rest of the time, while excessive activity or prolonged bed rest should be avoided. Daily dosing shall be conducted at the same time as far as possible. **Treatment and Observation Period (4 weeks after treatment)** Study drug: Administered once daily in the morning under fasting conditions for 4 consecutive weeks. Placebo: Administered once daily in the morning under fasting conditions for 4 consecutive weeks.
Examination Items and Time in Screening Period	The screening physical examination will be performed on D-56–D-1 of administration, and the screening examination items include the following: Measurement of height and weight; vital signs; physical examination; HbA1c (only in diabetics and when needed); hematology; blood biochemistry; chest X-ray (PA view); urinalysis; four coagulation tests; thyroid function; ANA test; blood pregnancy test (for females only); abdominal B-scan ultrasonography (liver, gallbladder, pancreas, spleen and both kidneys); Fibroscan; MRI-PDFF; infectious disease screening; and 12-lead electrocardiogram (ECG)

	examination. Results of infectious disease screening, chest X-ray, and abdominal B-scan ultrasonography obtained within 1 month before screening will be considered valid. MRI-PDFF results obtained within 8 weeks before screening will be regarded as screening examination results and no additional examination will be required.
Examination Items and Time at the End of Run-in Period (D-1)	Examination items at the end of the run-in period (D-1) include the following: Vital signs; physical examination; body weight measurement; hematology; blood biochemistry; urinalysis; four coagulation tests; Fibroscan; MRI-PDFF; blood pregnancy test (for females only); 12-lead ECG; urine drug screening; and alcohol breath test. For patients with MRI-PDFF, Fibrocan, hematology, blood biochemistry, urinalysis, and four coagulation test reports within 7 days before the first dose (D-7–D-1), it will be unnecessary to perform these examinations again on D-1.
Inclusion Criteria	**Subjects are eligible for the study only if all of the following inclusion criteria are met:** 1) Subjects aged ≥ 18 and ≤ 65, male or female; 2) Body mass index (BMI) ≥ 25 kg/m^2 at screening; 3) Subjects fulfilling the following criteria: a) ALT level exceeds the upper limit of normal once within 3 months (ALT elevation without other obvious reasons); b) Mean liver fat content ≥ 10% during screening and at the end of the run-in period (MRI-PDFF); 4) Stable body weight (defined as weight gain or loss ≤ 5%) 4–8 weeks pre-dose; 5) Pre-dose blood pressure: Systolic blood pressure ≤ 160 mmHg and diastolic blood pressure ≤ 95 mmHg (oral antihypertensive drugs can be taken regularly); 6) Maintain the same medication and lifestyle (diet and/or exercise) as those at enrollment during the trial; 7) Subjects who have no birth plan from screening to 6 months after the last dose and voluntarily take reliable contraceptive measures; 8) Subjects who fully understand the purpose and requirements of the trial, voluntarily participate in the clinical trial, and sign the written ICF, and are able to complete all trial processes according to the trial requirements.
Exclusion Criteria	**Those who meet any of the following criteria cannot be enrolled in this study:** 1) Subjects with a known history of allergies to the test product, any of its components, or related products; as well as those with allergic diseases or an allergic constitution; 2) Subjects with heavy alcohol consumption for 3 consecutive months or above within 1 year before screening. "Heavy alcohol consumption" is defined as average daily alcohol consumption of > 20 g for females and > 30 g for males, or uncontrollable alcohol consumption; 3) Subjects with cirrhosis suggested by liver biopsy or clinically diagnosed cirrhosis;

	4) Subjects with other concomitant liver diseases, including but not limited to drug-induced liver disease, alcoholic liver disease, autoimmune liver disease, hemochromatosis, Wilson's disease, suspected or confirmed liver cancer; 5) Subjects who have received liver transplantation surgery or plan to have this surgery: 6) Subjects who have received bariatric surgery or plan to have this surgery during the study; 7) Subjects with type 1 diabetes and poorly controlled type 2 diabetes (HbA1c > 10.5% at screening); 8) Patients with diabetes who use hypoglycemic drugs other than metformin; 9) Subjects with a history of malignant tumor within 5 years before screening (Note: 1. Subjects with cervical carcinoma *in situ* whose lesions have been resected and with no evidence of recurrence or metastasis for at least 3 years may participate in this study. 2. Subjects with basal cell or squamous cell carcinoma whose lesions have been completely resected and with no recurrent lesions for at least 3 years can participate in this study; 10) Subjects with serious cardiovascular and cerebrovascular events within 6 months before screening, including but not limited to uncontrolled or serious arrhythmia (ventricular fibrillation, atrial fibrillation, etc.), angina unstable, acute myocardial infarction, cardiac failure congestive, coronary intervention (including coronary artery stent implantation, intracoronary thrombectomy, and percutaneous transluminal coronary angioplasty, etc) or coronary artery bypass surgery, peripheral vascular intervention, stroke (except lacunar infarction), and transient ischaemic attack; 11) Subjects with gastrointestinal diseases or postoperative conditions affecting drug absorption; 12) Subjects who are taking drugs that may cause steatosis/steatohepatitis; 13) Subjects who have used ACLY-targeted drugs (Nexletol, etc.) and other study drugs, are taking statins (lovastatin, simvastatin, pravastatin, mevastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, pitavastatin, etc.), fibric acids (such as fenofibrate, gemfibrozil), probucol, warfarin, systemic steroids, cyclosporin or other immunosuppressants, or have taken these drugs less than 1 month or 5 half-lives of the drug (whichever is longer) from the first administration of the study drug; 14) Subjects who have used drugs with potential therapeutic effects on NASH (such as GLP-1 receptor agonists, DPP4 inhibitors, SGLT2 inhibitors, or other drugs known to affect liver function and cause steatosis at the discretion of the investigator) during the trial period and within less than 1 month from the screening; 15) Subjects with a TG > 6.0 mmol/L, direct bilirubin > 2 × ULN, creatinine clearance < 60 mL/min (calculated using the Cockcroft-Gault formula); 16) Platelet count < 75×10^9/L; 17) Subjects with confirmed positive and clinically significant results for antinuclear

	antibody (ANA) at screening; 18) Subjects with a history of hypothyroidism, hyperthyroidism, or subclinical thyroid disease (except for those with TSH levels < 10 mu/l, normal free T3 and T4 levels, and no symptoms of hypothyroidism); 19) Subjects with contraindications to MRI scan; 20) Subjects with blood donation or blood loss ≥ 400 mL within 3 months before screening; 21) Subjects who have participated in other drug clinical trials within 1 month prior to the screening; 22) Pregnant/lactating women or subjects confirmed positive in serum pregnancy test (female); 23) Subjects with positive results in urinary drug screening (morphine, marijuana); 24) Subjects who have consumed any food or beverage containing alcohol (or positive alcohol breath test result), grapefruit juice/grapefruit juice, methylxanthine (such as coffee, tea, cola, chocolate, and energy drink) within 1 day pre-dose, or have strenuous exercise or other factors affecting drug absorption, distribution, metabolism, and excretion; 25) Subjects with other severe systemic diseases unrelated to NASH; 26) Subjects infected with viral hepatitis (including hepatitis B and C), AIDS, or syphilis; 27) Subjects with high-risk factors of torsades de pointes (hypokalemia, hypomagnesemia, heart rate < 45 bpm), and ECG QTc interval longer than 490 ms during screening; 28) Subjects with other factors deemed by investigators as not suitable for the trial.
Concomitant Medication/Therapy	**Prohibited Drugs during the Study** During the administration period of clinical studies, the following medications are specifically prohibited unless required for adverse events: 1) All medications for the treatment of NASH other than this study drug are prohibited during the study. 2) During the study, other lipid-lowering drugs are prohibited (including but not limited to the following: Statins (lovastatin, simvastatin, pravastatin, mevastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, pitavastatin, etc.), fibric acids (such as fenofibrate, gemfibrozil), probucol, warfarin, systemic steroids, cyclosporin or other immunosuppressants). **Concomitant Drugs and Treatments as Appropriate in the Study** In addition to prohibited medications, the following medications/treatments are allowed as appropriate during the study: 1) Long-term medications required due to concomitant diseases before enrollment; 2) Symptomatic treatments for toxic reactions of drugs.
Criteria for	Subjects may withdraw from the trial at any time without providing a reason. Subjects

Treatment Discontinuation/Withdrawal	may withdraw from the trial under the following cases: 1) The subject requests to be withdrawn from the trial; 2) Serious violation of the protocol; 3) The subject becomes pregnant; 4) Subjects experience severe clinical or laboratory changes or intolerable adverse events, and continuing the trial will not be conducive to their health. These subjects may withdraw from the trial prematurely upon mutual agreement between the investigator and the sponsor; 5) Other circumstances warranting withdrawal as deemed necessary by the investigator, including subjects' poor adherence to medication intake or PK blood sampling. Regardless of the reason, safety and efficacy data for subjects who discontinued and withdrew from treatment should be obtained as much as possible. In any case, the reason for withdrawal from the study should be recorded in the study medical records and case report forms (CRFs), and all end-of-treatment assessments should be performed if the subject is willing and compliant.
Termination Criteria	Premature termination of trial means that the clinical trial is not completed for all subjects as per the protocol and the entire trial is stopped halfway. Termination mainly aims to protect the rights and interests of subjects, ensure the quality of the trial, and avoid unnecessary economic losses. Under normal circumstances, the trial will not be terminated prematurely at will. However, the entire trial may be terminated prematurely in any of the following cases: 1) New information is obtained, which leads to an unfavorable risk-benefit evaluation of the study drug, including sufficient evidence for lack of efficacy or unacceptable safety; 2) The sponsor believes that it is inappropriate to continue the clinical trial for medical, ethical or business reasons; 3) The enrollment of subjects is suboptimal, as a result, it is impossible to complete the trial within an acceptable time period; 4) NMPA or the Ethics Committee orders to terminate the trial for certain reasons. If the clinical trial is terminated prematurely, all parties involved (Sponsor, Investigator, Ethics Committee, clinical trial institution, and administrative authority) shall be notified in writing in a timely manner.
Elimination Criteria	Before statistical analysis of the data, statisticians and principal investigators should discuss whether to exclude individual cases. In any of the following circumstances, the principal investigator should comprehensively judge whether to reject the subject according to the degree of completion of the trial, reasons for withdrawal, and other factors, and make relevant explanations:

	1) The selection of individual subjects violates the inclusion/exclusion criteria; the investigator and the sponsor should jointly discuss whether the subject needs to be excluded. 2) During the trial, the subject fails to follow the trial protocol and has poor compliance; for example, the subject does not take the study drug or fails in sampling for pharmacokinetic, pharmacodynamic, and safety evaluation as required by trial protocol, or presents no data. 3) During the trial, the investigator considers that subjects have other factors indicating unsuitability for further trial and terminates their participation.
PK Sampling and Assessment	**PK Blood Collection Points:** On D1, 0 h pre-dose (within 60 min pre-dose) and 10 min (±0.5 min), 20 min (±0.5 min), 40 min (±1 min), 1 h (±1 min), 1.5 h (±1.5 min), 2 h (±1.5 min), 3 h (±3 min), 4 h (±3 min), 6 h (±6 min), 8 h (±6 min), 12 h (±12 min) and 24 h (±36 min) post-dose; Within 60 min pre-dose on D8, D15, D22, D26 and D27; On D28, 0 h pre-dose (within 60 min pre-dose) and 10 min (±0.5 min), 20 min (±0.5 min), 40 min (±1 min), 1 h (±1 min), 1.5 h (±1.5 min), 2 h (±1.5 min), 3 h (±3 min), 4 h (±3 min), 6 h (±6 min), 8 h (±6 min), 12 h (±12 min) and 24 h (±36 min). According to the PK data results of the completed dose groups in this project, the sponsor and the investigator decided after discussion to adjust the blood collection time points for 100 mg, 150 mg, and 200 mg (alternative) dose groups by adding 4 new PK blood collection points: 72 h (±1 h, D31), 168 h (±2 h, D35), 240 h (±2 h, D38) and 312 h (±2 h, D41) post-dose on D28. **PK Assessment** Evaluation of PK parameters for BGT-002 and its metabolites (if applicable) will include: Evaluation of PK parameters on Day 1 (D1): C_{max}, T_{max}, AUC_{0-24h}, etc.; Evaluation of steady-state PK parameters (D28): $C_{max,ss}$, $T_{max,ss}$, AUC_{ss}, CL_{ss}/F, $C_{min,ss}$, R_{ac}, etc.
Collection and Assessment of PD and Exploratory Indicators	**Imaging PD Indicators and Examination Time Points:** MRI-PDFF: D-1 (for subjects with results within 7 days pre-dose, examination may be omitted on D-1), D29/early withdrawal (+5 days), and D56 (± 5 days). CAP and LSM: D-1 (for subjects with results within 7 days pre-dose, examination may be omitted on D-1), D29/early withdrawal, and D56 (± 5 days). **Other PD Indicators and Collection Points:** BMI, ALT, AST, TG, LDL, and TC: D-1, D29/early withdrawal, and D56 (± 5 days); **Exploratory Indicators (Test Indicators Adjusted According to the Actual Situation of Testing Unit) and Collection Points:** CK18, FGF21, IP10, hsCRP, TIMP1, and β-HB: 0 h pre-dose on D1 (within 60 min pre-dose), 24 h (+36 min) post-dose on D28, and D56 (± 5 days).

	Primary Efficacy Variables: Changes from baseline in ALT, AST, BMI and blood lipid levels at Week 4 and Week 8; Change from baseline in liver fat content measured by MRI-PDFF at Week 4 and Week 8; Proportion of subjects with a relative reduction of at least 30% in liver fat content measured by MRI-PDFF at Week 4 and Week 8; **Secondary Efficacy Variables:** Changes from baseline in CAP and LSM at Week 4 and Week 8; **Exploratory Evaluation Indicators:** Changes from baseline in biomarkers (CK18, FGF21, IP10, hsCRP, TIMP1, β-HB) at Week 4 and Week 8.
Tolerability and Safety Evaluation Indicators	The safety and tolerability of BGT-002 in subjects after administration will be evaluated. Adverse events (AEs) throughout the study will be evaluated and graded according to CTCAE 5.0. The indicators will include symptoms and physical examination, clinical laboratory tests (hematology, coagulation function, blood chemistry and urinalysis), vital signs (blood pressure, pulse, respiration and body temperature) and 12-lead ECG. **C-QTc Study:** To investigate the effect of BGT-002 in 75 mg, 100 mg, 150 mg, and 200 mg (alternative) dose groups on QT/QTc interval in subjects, a C-QTc study will be conducted for 36-48 subjects on D1 and D28.
Statistical Analysis	**Analysis Population** Full Analysis Set (FAS): Randomized subjects who received at least 1 dose of the study drug with safety data available. Safety Set (SS): Randomized subjects who received at least 1 dose of the study drug. Pharmacokinetics Set (PKS): Randomized subjects who received at least 1 dose of the study drug with at least one evaluable PK concentration data. The inclusion of subjects in the PKS will be determined on a case-by-case basis at the data verification meeting. Pharmacodynamics Set (PDS): Randomized subjects who received at least 1 dose of the study drug with at least one valid PD evaluation data. The inclusion of subjects in the PDS will be determined on a case-by-case basis at the data verification meeting. **Statistical Methods** Descriptive statistical analysis will be mainly adopted for the trial results. For quantitative indicators, the mean, standard deviation, median, maximum, and minimum values will be listed. Frequency (constituent ratio) will be presented for enumeration data and ranked data. The inclusion, completion, and early withdrawal of subjects in each dose group will be described, and the demographic and baseline characteristics of

randomized/enrolled subjects will be summarized. The number and percentage of subjects included in different analysis data sets will be calculated for each dose group.

Statistical Analysis of C-QTC Study:

Exploratory statistical analysis will be performed on C-QTc based on PK and QT interval changes. Descriptive analysis will be performed for QT/QTc intervals and changes from baseline at each time point, and line charts will be used to depict the changes at each time point and between groups. Baseline correction (ΔQTc) and placebo correction (ΔΔQTc) will be applied to the obtained QT/QTc intervals, with ΔQTc as the dependent variable to measure the degree of drug effect on QT/QTc. The changes in drug concentration and QT/QTc intervals will be considered for model-based exploratory analysis.

Tolerability and Safety Evaluation:

Statistical analysis will be performed using SAS (v9.4 or above).

Adverse events (AEs) will be coded as per the Medical Dictionary for Regulatory Activities (MedDRA). The AEs observed during the trial will be described by system organ class (SOC) and preferred term (PT) for each dose group. Descriptive statistics of clinical laboratory tests, 12-lead ECGs, C-QTc study, vital signs, and physical examination results will be performed for each dose group. Clinically significant changes in clinical laboratory findings from baseline will be presented in the shift table.

Evaluation of the C-QTc study: The threshold of concern is a ΔΔQTc interval prolongation exceeding 5 ms. Based on the C-QTc study results, it can be confirmed whether the conditions for conducting a TQT study are met. According to the C-QTc model, if the upper limit of two-sided 90% CI for ΔΔQTcF corresponding to the highest clinical exposure is ≤ 10 ms, it can be considered that the mean QT/QTc effect of the drug is not more than 5 ms, and the C-QTc study result is negative. However, if the upper limit of two-sided 90% CI for ΔΔQTcF corresponding to low clinical exposure is > 10 ms by model calculation, the C-QTc study result will be positive. When the upper limit of two-sided 90% CI for ΔΔQTcF corresponding to low clinical exposure is ≤ 10 ms and the upper limit of two-sided 90% CI for ΔΔQTcF corresponding to the highest clinical exposure is > 10 ms, the dose range for negative ΔΔQTcF (≤ 10 ms) can be obtained with the model.

Pharmacokinetic Analysis:

Plasma concentrations will be summarized by dose group and scheduled sampling time point, including the number of subjects, the number of subjects below the quantification limit (BQL), arithmetic mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation. Individual and mean plasma concentration-time (C-T) curves will be plotted separately.

Based on the non-compartmental model, Phoenix WinNonlin software (Certara USA Inc, version 8.2 or above) will be used to calculate PK parameters (main PK parameters include T_{max}, C_{max}, and AUC). PK parameters will be summarized by dose group, including the number of subjects, arithmetic mean, standard deviation, median, minimum, and

	maximum. For PK parameters, other than T_{max}, the coefficient of variation (CV, based on the arithmetic mean), geometric mean, and geometric CV will also be derived. Descriptive statistics of main PK parameters post-dose will be performed using the Statistical Analysis Software (SAS, v9.4 or above) for each dose group, including a comparison of T_{max} between groups using a non-parametric test. An exploratory analysis of PK parameters (AUC and C_{max}) versus dose will be conducted for potential dose proportionality. The relationship of log-transformed PK parameters against the log-transformed dose (fixed effect) will be fitted using the Power model to calculate the slope (β) and its 90% confidence interval (CI) on the log scale. **Pharmacodynamic Analysis** Descriptive statistics will be used to calculate and summarize the changes from baseline in liver fat content measured by MRI-PDFF at 4 weeks and 8 weeks, the proportion of subjects with a relative reduction of at least 30% in liver fat content measured by MRI-PDFF, the changes from baseline in ALT, AST, BMI, blood lipid levels, and the changes from baseline in CAP and LSM for each group. **Analysis of Exploratory Indicators** Descriptive analysis will be performed for exploratory biomarker indicators (CK18, FGF21, IP10, hsCRP, TIMP1, and β-HB) after administration in each dose group to explore the relationship between dose/exposure and effect of BGT-002. The specific statistical methods are specified in the Statistical Analysis Plan.