A study to evaluate the safety, tolerability, and pharmacokinetic profile of single or multiple oral doses of ABSK061 microt and to evaluate the effect of soft food with ABSK061 microchips on its pharmacokinetic profile in healthy adult participants

Protocol No.: ABSK061-102
Trial Phase: phase I
Sponsor: shanghai Hezhu Biopharmaceutical Technology Co., Ltd.
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Version No.: 1.0
Version Date: april 7, 2025

The study will be conducted in strict compliance with the protocol and will be designed in compliance with GCP, the Declaration of Helsinki, and other applicable laws and regulations.

Sponsor Signature Page

_____ _____

Jing Nie **Date**

Senior Director, Clinical Pharmacology

Investigator Signature Page

I have understood that all study-related documents provided to me by Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. or its designated third party will be kept strictly confidential, including the protocol, Investigator's Brochure, case report forms, and other scientific data.

The study will not commence without written approval from the Institutional Review Board (IRB)/Ethics Committee (EC). No amendments to the protocol may be made without written approval from Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. and the Ethics Committee, unless necessary to protect participants and eliminate direct hazards.

I have read, understand and agree to comply with all the conditions and instructions in this clinical study protocol.

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Investigator Signature **Date**

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Site Name

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Protocol Synopsis

Protocol Title	A study to evaluate the safety, tolerability, and pharmacokinetic profile of single or multiple oral doses of ABSK061 microt and to evaluate the effect of soft food with ABSK061 microchips on its pharmacokinetic profile in healthy adult participants
Protocol Number	ABSK061-102
Study Phase	Phase 1
Study drug	ABSK061
Number of samples	Part I: 18 healthy participants enrolled (6/sequence) Part II: 12 healthy participants enrolled (6/sequence) Part III: 12 healthy participants enrolled (4/sequence)
Study Objectives	**Primary Objective:** • Part I: to evaluate the pharmacokinetic profile (PK) and safety of a single oral dose of ABSK061 microchip in healthy adult participants; • Part II: to evaluate the safety, tolerability, and PK profile of multiple oral doses of ABSK061 microt in healthy adult participants. • Part III: to evaluate the effect of ABSK061 microt 5 mg administered with soft food on the PK profile of ABSK061. **Secondary objectives:** 1. To assess the safety of ABSK061 microchips taken with soft food in healthy adult participants; 2. To explore the dose-exposure proportionality of 1 to 35 mg of ABSK061 microchips in healthy adult participants.
Study Endpoints	**Primary endpoint:** • Safety and tolerability evaluation indicators, including adverse events (AEs), serious adverse events (SAEs), vital signs, physical examinations, electrocardiograms, laboratory tests, ophthalmic examinations, etc.; • Main PK parameters of ABSK061 micro-tablets, including maximum observed concentration (Cmax), time to reach maximum observed concentration (tmax), area under the plasma concentration-time curve (AUClast and AUC0- ∞), maximum observed concentration during the steady-state dosing interval (Cmax, ss), minimum observed concentration during the steady-state dosing interval (Cmin, ss), area under the concentration-time curve at steady-state dosing interval (AUCtau, ss), and accumulation index (AR);

<table>
<tr><td></td><td>
• PK parameters, mainly including Cmax, AUC0- ∞, and AUClast, following a single dose of ABSK061 microt administration with or without soft food.
Secondary endpoints:
• Secondary PK parameters of ABSK061: including but not limited to terminal elimination half-life (t1/2), apparent clearance (CL/F), and apparent volume of distribution (Vz/F).
</td></tr>
<tr><td>Study Design</td><td>
The study consists of three parts: Part I, Part II and Part III. Part II and Part III will be performed in parallel after completion of Part I.
Part I
Part I is a single-dose PK study with the primary objective of evaluating the PK profile and safety of ABSK061 in healthy participants after a single dose. A total of 18 healthy participants were planned to be enrolled in Part I and randomized 1: 1: 1 to Sequences A, B, and C. Participants in three sequences received A single microchip dose of ABSK061 at doses of 1 mg, 10 mg, and 35 mg, respectively, followed by A 7-day safety observation (until D8).
All participants will take ABSK061 microchips with 180 mL of water under fasting conditions. The study design is shown in Table 1 Part I Test Design.
Table 1 Part I Study Design
<table>
<tr><th></th><th>D1</th><th>D8</th></tr>
<tr><td>Sequence A</td><td>1 mg</td><td rowspan="3">End of Safety Observations</td></tr>
<tr><td>Sequence B</td><td>10 mg</td></tr>
<tr><td>Sequence C</td><td>35 mg</td></tr>
</table>
Part II
Part II is a multiple dose escalation (MAD) study with the primary objective to evaluate the tolerability, safety and PK profile of ABSK061 microchips in healthy participants after multiple doses. A total of 12 healthy participants were planned to be enrolled in Part II, with multiple dose escalation trials prespecified in Sequences D and E, with 6 healthy participants in each sequence. In this MAD study, participants in Sequence D received ABSK061 microchips 5 mg QD for 4 consecutive days with 14-day safety observations starting after the last dose (D5 to D18); the investigator and sponsor will decide whether to adjust the next dose level, Sequence E, based on the available safety data and PK data during the Sequence D trial. Healthy participants in Sequence E received ABSK061 microchips at 20 mg QD for 4 consecutive days, as well as 14-day safety observations starting after the last dose (D5 to D18).
All participants will take ABSK061 microchips with 180 mL of water under fasting conditions. The study design is shown in Table 2 Part II Study
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</table>

Design Table 2 Part II Study Design.

Table 2 Part II Study Design

	D1	D2	D3	D4	D18
Sequence D	5 mg QD	5 mg QD	5 mg QD	5 mg QD	End of Safety Observations
Sequence E	20 mg QD	20 mg QD	20 mg QD	20 mg QD	End of Safety Observations

Part III

Part III is a three-period, three-sequence crossover study with the primary objective to evaluate the effect of co-administration of soft food on the PK of ABSK061. Part III plans to include 12 healthy participants randomized 1: 1: 1 to Sequence F, Sequence G, or Sequence H to receive a single oral dose of ABSK061 in triplicate doses of Treatment 1, Treatment 2, Treatment 3. Treatment 1 was 5 mg ABSK061 microchip taken with 180 mL of water, Treatment 2 was 5 mg ABSK061 microchip taken with a spoon of yogurt (approximately 15 mL), and Treatment 3 was administered with 5 mg ABSK061 microchip with a spoon of applesauce (approximately 15 mL). Participants in Sequence F will receive Treatment 1, Treatment 2, and Treatment 3 under fasting conditions in the morning on Cycle 1 Day 1 (D1), Cycle 2 Day 1 (D4), and Cycle 3 Day 1 (D7), respectively; participants in Sequence G will receive Treatment 2, Treatment 3, and Treatment 1 in the morning on D1, D4, and D7, respectively; participants in Sequence H will receive Treatment 3, Treatment 1, and Treatment 2 fasted in the morning on D1, D4, and D7, respectively. All participants were required to drink 180 mL of water immediately after swallowing the investigational drug. The washout period for each period was 3 days. The study design is shown in Table 3 Part III Study Design.

Table 3 Part III Study Design

	Cycle 1	Cycle 2	Cycle 3
Sequence F	Treatment 1	Treatment 2	Treatment 3
Sequence G	Treatment 2	Treatment 3	Treatment 1
Sequence H	Treatment 3	Treatment 1	Treatment 2

Note: Treatment 1: 5 mg ABSK061 micro-tablets were administered with 180 mL of water; treatment 2: 5 mg ABSK061 microchip + 1 tablespoon yogurt; treatment 3: 5 mg ABSK061 microchips + 1 tablespoon of applesauce. The washout period of each cycle was 3 days.

Investigational Product	ABSK061 capsules were manufactured and provided by the sponsor in two strengths: 0.2 mg/capsule, containing 4 0.05 mg tablets; 5 mg/capsule containing 10 0.5 mg tablets.
Mode of	The 1 mg dose corresponds to 5 capsules of the 0.2 mg strength, the 5 mg dose corresponds to 1 capsule of the 5 mg strength, the 10 mg dose

administration	corresponds to 2 capsules of the 5 mg strength, the 20 mg dose corresponds to 4 capsules of the 5 mg strength, and the 35 mg dose corresponds to 7 capsules of the 5 mg strength. The ABSK061 cap was opened prior to dosing and the microt was poured out and swallowed. See Section 7.6 Investigational Product Administration for details. Part I&II: dosing was administered under fasting conditions and participants were required to fast overnight for at least 10 hours until the next morning. Water deprivation (except for water for drug administration) from 1 hour before dosing to 1 hour after dosing. All participants received ABSK061 microchips directly with 180 mL of water (see Table 1 Part I trial design and Table 2 Part II trial design), and no food was allowed for 4 hours after dosing. Part III: dosing was administered under fasting conditions, with participants fasting overnight for at least 10 hours until the next morning. Water deprivation (except for water for drug administration) from 1 hour before dosing to 1 hour after dosing. See Table 3 Part III Study Design. Participants receiving Treatment 1 received 10 0.5 mg ABSK061 microchips directly with 180 mL of water, and no food was allowed within 4 hours after dosing; Participants receiving Treatment 2 dispersed 10 0.5 mg tablets on 1 tablespoon of yogurt (approximately 15 mL) and swallowed together, followed by 180 mL of water immediately, and no food was allowed for 4 hours after dosing; Participants receiving Treatment 3 swallowed 10 0.5 mg tablets sprinkled on 1 tablespoon of applesauce (approximately 15 mL), followed by 180 mL of water immediately, and no food was allowed for 4 hours after dosing.
PK blood sampling	Plasma samples were collected from all participants in this study before and after dosing to determine the concentrations of ABSK061 and its metabolites (if applicable) for PK assessment. The specific collection times are detailed in Table 7 Part I PK sampling times, Table 8 Part II PK sampling times, and Table 9 Part III PK sampling times. The requirements for blood sampling and blood sample processing are provided in the Central Laboratory Manual.
Inclusion/Exclusion Criteria	**Inclusion criteria:** 1) Gender: male or female participants, both male and female; 2) Age: 18 to 45 years (including 18 and 45 years); 3) Weight: male participants weigh ≥ 50.0 kg, female participants weigh ≥ 45.0 kg, and body mass index is in the range of 19.0-26.0 kg/m2 (including cut-off value), and body mass index (BMI) = weight (kg)/height 2 (m2); 4) Able to understand and willing to comply with the study procedures, voluntarily participate in this clinical trial and sign the informed consent form before screening; 5) Male or female participants of childbearing potential must agree to use effective methods of contraception during the study and for 6 months after the last dose of investigational product (see Section 5.5 Pregnancy Restrictions for details) and that male participants do not donate sperm

during this period; female participants do not donate eggs during this period and must be non-pregnant, non-lactating female participants, defined as women after conception until termination of pregnancy, and human chorionic gonadotropin (β-HCG) is within the normal range.

Exclusion criteria:

1) History of bacterial, fungal, parasitic, viral (excluding nasopharyngitis), mycobacterial infection, COVID19 infection within 30 days prior to screening;
2) Prolongation of QT interval corrected for heart rate at screening, QTcF > 450 ms (Note: QTc interval corrected by Fridericia ' s formula), or family history of long QT syndrome;
3) Any of the following ophthalmic exclusion criteria:
   - Current or past medical history of retinal pigment epithelial detachment (RPED)/central serous retinopathy (CSR)
   - Previous laser therapy or intraocular injection for macular degeneration
   - Current concomitant or past medical history of age-related macular degeneration
   - Current concomitant or past medical history of retinal vein occlusion (RVO)
   - Current concomitant or past medical history of retinal degenerative disease
   - Diabetic retinopathy with macular edema
   - Current concomitant or past medical history of any other clinically relevant retinal-choroidal defect
   - Any symptoms of acute ophthalmic disease (within 4 weeks prior to the first dose) or active progression
   - Current concomitant keratopathy (eg, keratitis, corneal abrasion, or ulceration) or conjunctivitis
4) Subjects with a history of motor system, neuropsychiatric system, endocrine system, blood circulation system, respiratory system, digestive system, urinary system, reproductive system abnormalities, etc., or existing diseases, which may affect the assessment of study results;
5) Prior history of gastric or intestinal surgery, or surgery affecting drug absorption, distribution, metabolism, excretion (except for appendicitis surgery); or plan to undergo surgery during the study;
6) Donation of blood or massive blood loss (≥ 400 mL) within 3 months prior to screening or during screening (except for female physiological period); those who have received blood transfusion or blood products within 2 months prior to screening;
7) History of drug abuse or positive urine drug screen (morphine, tetrahydrocannabinol acid, methamphetamine,

	dimethyldioxyamphetamine, ketamine) within the past 5 years; 8) Those who are allergic to drugs, environment or food or to ABSK061 micro-tablets or its excipients [microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, film-coating premix (gastric soluble)]; those who are prone to allergic symptoms such as rash and urticaria; for Part III: previously known allergies to yogurt and applesauce foods; 9) Previous chronic consumption of excessive tea, coffee, or caffeinated beverages (defined as ingestion of more than 6 units of caffeine per day, 1 unit of caffeine equivalent to 177 mL of coffee, 355 mL of tea, 355 mL of cola, or 85 grams of chocolate) or who cannot stop drinking any caffeinated beverage during the trial; 10) Those who consumed more than 14 units of alcohol per week (1 unit = 360 mL of beer or 45 mL of spirits containing 40% alcohol or 150 mL of wine), or were unable to abstain from alcohol during the trial, or had an alcohol breath test result > 0 mg/100 mL within 3 months prior to signing the informed consent form; 11) Smoking ≥ 5 cigarettes per day before signing the informed consent form; or cannot stop using any tobacco products during the trial; 12) Those who have taken strong CYP3A4 inhibitors or inducers (including grapefruit juice, grapefruit hybrids, pomegranates, carambola, grapefruit, Seville oranges and fruit juices or other processed products within 14 days prior to screening and during the screening period, as detailed in Appendix 12.1 Strong CYP3A inducers and inhibitors); 13) Those who have special requirements for diet and cannot comply with the unified diet; specific dietary requirements were: (i) only meals provided by the study site during hospitalization, and (ii) avoidance of strong CYP3A4 inhibitors or inducers during the study; 14) Dysphagia, inability to take the investigational product orally; 15) Lactose intolerance (those who have had milk diarrhea); 16) Those who have used any prescription drugs, over-the-counter drugs, Chinese herbal medicines or health products within 14 days prior to the first dose or plan to use them during the study; 17) Those who have received vaccines (including COVID19 vaccine) within 2 months prior to screening, or have planned vaccination throughout the study; 18) Previous participation as a participant in any other ABSK061-related study and has taken any dosage form of ABSK061; those who have participated in other clinical trials and used other clinical investigational drugs or investigational devices within 3 months prior to screening or during screening, or who plan to participate in other clinical trials during this study, or who are not self-participating in clinical trials; 19) Those with a history of needle sickness, blood sickness or intolerance to

	venipuncture, or difficulty in blood collection; 20) Abnormal physical examination, hematology, blood chemistry, coagulation function, urinalysis, 12-lead electrocardiogram, chest X-ray (anteroposterior), abdominal B-ultrasound, ophthalmic examination and judged by the investigator to be clinically significant; 21) Vital signs outside the normal range, and the retest is still outside the normal range. 22) Abnormal serum hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody, treponema pallidum antibody test and judged by the investigator to be clinically significant; 23) Personnel involved in the design or implementation of this study project and their immediate family members (e.g., employees of Shanghai Hezhui Biopharmaceutical Technology Co., Ltd., CRO employees, and employees of the study site); 24) Any other factor that, in the opinion of the investigator, is not suitable for enrollment, may affect the compliance of the participant with the protocol, affect the interpretation of the study results, or increase the participant's safety risk, or the participant withdraws from the trial for his/her own reasons.
Statistical Methods	No formal statistical hypothesis testing will be performed in this study. All analyses were mainly descriptive, and the primary analysis set included the PK concentration analysis set, the PK parameter analysis set, and the safety analysis set. Pharmacokinetic parameters of ABSK061 in capsules will be calculated and analyzed by a standard noncompartmental model. Results of PK parameters and summary data will be provided for each participant. Descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation) were calculated for all PK parameters except tmax, which will summarize the median, minimum, and maximum. Data listings for all PK parameters will be provided. The PK profile of single or multiple oral doses of ABSK061 microt was assessed based on the main PK parameters obtained, the effect of oral administration with soft food on the pharmacokinetics of ABSK061, and the dose-exposure proportionality of ABSK061 microt was explored. Specific PK parameters include, but are not limited to, total drug exposure (AUC0- ∞, AUClast), maximum concentration (Cmax), time to maximum concentration (tmax), elimination half-life (t1/2), apparent clearance (CL/F) and apparent volume of distribution (Vz/F), accumulation ratio (AR). Part III evaluated the effect of co-administration of soft food on the PK characteristics of ABSK061, and natural log-transformation was performed on

	the main PK parameters (AUC0- ∞, AUClast, Cmax), and the Geometric Least Squares mean Ratio (Ratio in Geometric Least Squares Means, RGLSM, administered with soft food/water) was obtained by linear mixed model for statistical analysis and antilogarithmic transformation, and intra-individual coefficient of variation was calculated for each parameter. The dose-exposure proportionality of ABSK061 administered as capsules in fasted water will also be explored by graphical presentation of primary PK parameters (AUC0- ∞, AUClast, Cmax) and/or dose-normalized primary PK parameters. If applicable, the dose-exposure proportionality will be further explored through the Power model by natural log-transformation of the primary PK parameters. The safety analysis set will be used for safety analysis. Safety will be assessed based on AE reporting, clinical laboratory data, vital signs, and electrocardiograms. Missing safety data will not generally be imputed unless otherwise specified.
End of Study Criteria	A participant is considered to have completed the study if he/she has completed all visits to the study, including the last visit or last trial procedure shown in the flowchart. The end of study was defined as the completion of all procedures in the last visit or flowchart for the last participant (including safety telephone follow-up).
Study Duration	Including screening period (and baseline period), trial period and safety observation period/follow-up period: Screening + Baseline: 14 days; Part I: the single-dose PK study included a single dose (1 day) and a safety observation period (7 days); part II: the multiple dose escalation PK study included multiple doses (4 days) and a safety observation period (14 days); Part III consists of three cycles (3 days per cycle for a total of 9 days) and a safety observation period (7 days).

Study Flow Chart

Table 4 Part I Study Plan (Single Dose)

Study Procedures	Screening 1	Baseline	Study Period 2			Follow-up 3	Early Withdrawal 4
	D-14 ~D-2	D-1	D1	D2	D3	D8 (+ 3 days)	
Signed informed consent	×						
Eligibility Criteria	×	×					
Demographic Data 5	×						
Medical history 6	×						
Vital Signs 7	×	×	×	×	×		×
Physical Examination 8	×				×		×
Height and weight 9	×						
Hematology 10	×	×			×		×
Urinalysis 11	×	×			×		×
Blood Chemistry 12	×	×			×		×
Coagulation 13	×	×			×		×
Virology 14	×						
Chest X-ray (anteroposterior) 15	×						
Abdominal ultrasonography (liver, gallbladder, pancreas, spleen, kidney) 16	×						
12-lead ECG 17	×	×	×		×		×
Blood pregnancy test 18	×	×			×		×
Drug abuse screening 19		×					
Alcohol breath screen		×					
Ophthalmic Examination 20	×				×		×
Randomization		×					
Admission to study ward		×					
Taking ABSK06121			×				
PK blood sampling 22			×	×	×		×
Leave study ward					×		×
Telephone follow-up						×	
Adverse Events 23	×						
Prior and concomitant medications 24	×						

Instructions:

1. Screening: all assessments at screening should be completed within 14 days prior to the first dose of investigational product. If screening cannot be completed on time, the sponsor should be contacted to determine if the screening process performed prior to dosing is repeated. All screening examinations must be completed at this site. If a laboratory value at screening does not meet the participant selection criteria, only up to one retest that is judged by the investigator to be required during the screening period is allowed. If the retest value still does not match, the participant should be excluded.
2. Study period: dosing on Day 1 (D1) and washout from D1 to D3 were included. Participants should be admitted to the clinical study ward of the study site on the day prior to dosing (i.e., D-1), eat uniformly, and undergo relevant visit examinations. Participants cannot leave the clinical study ward of the study site during the trial.
3. Participants should be contacted by telephone follow-up on D8 (+ 3 days) 7 days after administration of ABSK061 and information on adverse events and concomitant medications should be collected.
4. Early withdrawal applies to participants who have received ABSK061 and will no longer be followed for safety.
5. Demographic data will include gender, ethnicity, and date of birth of the participant.
6. Medical history inquiry: including past medical history and treatment history, smoking history, alcohol consumption history, drug allergy history, food allergy history, concomitant diseases and treatment. The inquiries are detailed in Protocol 8.3.1 Demographics and Disease History.
7. Vital signs included ear temperature, sitting blood pressure, respiratory rate, and pulse rate. Vital signs are recommended after the participant has rested quietly for at least 5 minutes. Vital signs should be measured at 1 hour (± 1 hour) pre-dose, 2 hours (± 1 hour) post-dose, 6 hours (± 1 hour) post-dose, 24 hours (± 1 hour) post-dose, 48 hours (± 1 hour) post-dose, and at the Early Withdrawal Visit. Vital signs should be performed prior to PK blood sampling or at least 20 min apart after PK blood sampling. Additional vital sign testing may be added during each study at the discretion of the investigator. If the vital signs test results at screening are not within the normal range, they may be repeated once, and if they are still not within the normal range, the screening fails; participants who have been assigned a random number may be retested once if their vital signs test results are not within the normal range prior to the first dose on D1, or drop out if they are still outside the normal range and judged by the investigator to be clinically significant.
8. Physical examination: a complete physical examination is required at screening or baseline, and only a general physical examination will be performed during subsequent studies. A complete physical examination included mucocutaneous, lymph nodes, head, neck, chest, abdomen, spine, extremities, and nervous system. General physical examination, which may include head and neck, chest and abdomen, will be determined by the investigator as clinically indicated.
9. Height and weight: collected at Screening or Baseline only. Investigators may perform more frequent tests if clinically indicated.
10. Hematology: including red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT) and total platelet count (PLT), white blood cell count (WBC) with differential and proportion (including neutrophil percentage and absolute neutrophil percentage, lymphocyte percentage and absolute lymphocyte count, monocyte percentage and absolute monocyte count, eosinophil percentage and absolute eosinophil percentage, basophil percentage and absolute basophil percentage). If hematology at screening is performed within 7 days prior to the first dose, hematology will not be performed separately at baseline on D-1.
11. Urinalysis: including specific gravity, glucose, protein, ketones, occult blood, and red blood cells. Participants with significant clinical findings should be further evaluated. If urinalysis at screening is performed within 7 days prior to the first dose, urinalysis will not be performed separately at baseline on D-1.

12. Blood chemistry: includes total bilirubin, direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), lactate dehydrogenase, glucose, urea, creatinine, total cholesterol, triglycerides, potassium, sodium, chloride, calcium, phosphorus, magnesium, carbon dioxide. In the event of ≥ CT CA E2 transaminase elevations during the trial, more frequent liver function tests (at least twice weekly) will be required until recovery to Grade 1 or baseline. Additional laboratory tests may be performed if clinically indicated. If blood chemistry at screening is performed within 7 days prior to the first dose, blood chemistry will not be performed separately at baseline on D-1.

13. Coagulation: includes prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), plasma fibrinogen (Fbg), and thrombin time (TT). If coagulation at screening is performed within 7 days prior to the first dose, coagulation tests will no longer be performed separately at baseline on D-1.

14. Virology: including five tests for hepatitis B virus (HBV): hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), and hepatitis B core antibody (HBcAb); treponema pallidum antibody, hepatitis C virus antibody (HCV-Ab), human immunodeficiency virus antibody. If virology at screening is performed within 28 days prior to the first dose, virology will no longer be performed separately at Screening and Baseline.

15. Chest X-ray (anteroposterior) will be performed only once at screening or baseline and results within 3 months prior to signing the informed consent form are acceptable.

16. Abdominal B-ultrasound (liver, gallbladder, pancreas, spleen, kidney) will be performed only once at screening or baseline. If abdominal B-ultrasound at screening is performed within 28 days prior to the first dose, abdominal B-ultrasound will not be performed separately at screening and baseline.

17. 12-lead ECG: a 12-lead ECG will be performed once at screening and once at baseline on D-1. If the 12-lead ECG at screening is performed within 7 days prior to the first dose, 12-lead ECG will not be performed separately at D-1 baseline. A single 12-lead electrocardiogram was performed 1 hour (± 1 hour) before dosing on the day of dosing (D1), the day of leaving the ward (D3), and early withdrawal. The 12-lead ECG prior to dosing on the day of dosing should be performed prior to PK blood sampling, and the remaining 12-lead ECGs should be performed at least 45 minutes apart if required after invasive tests (e.g., PK blood sampling, etc.). Additional ECGs may be performed by the investigator as clinically indicated. The 12-lead ECG should include heart rate, RR interval, PR interval, QT interval, and calculation of QTcF. The specific examination requirements of 12-lead ECG are detailed in Protocol 8.3.4 12-lead ECG.

18. For female participants of childbearing potential, a blood pregnancy test is required at Screening, D-1 Baseline, and D3/Early Withdrawal. A blood pregnancy test is not required for women of non-childbearing potential. Women of non-childbearing potential were defined as postmenopausal (≥ 12 months postmenopausal) or had a documented bilateral tubal ligation, complete oophorectomy, or hysterectomy. If the blood pregnancy test at screening is performed within 2 days prior to the first dose, the blood pregnancy test will not be repeated at baseline on D-1.

19. The drug screen included morphine, ketamine, methamphetamine, dimethylene dioxyamphetamine, and tetrahydrocannabinol acid.

20. Ophthalmic Examination: participants were evaluated ophthalmologically by an ophthalmologist at Screening, D3/Early Withdrawal Visit. Each ophthalmologic assessment should be performed by the same ophthalmologist whenever possible. Specific examination requirements are detailed in 8.3.7 Ophthalmic Examination.

21. Taking ABSK061: the drug should be taken in a fasted state on Day 1 (D1). Refer to Section 7.6 for details.

22. The time windows for PK blood sample collection are detailed in Table 7 Part I PK sampling times.
23. Adverse events will begin when the participant signs the informed consent form until 7 days after administration of ABSK061 (i.e., D8), as detailed in 8.3.13 Safety Reporting Period.
24. Concomitant medication information was collected from the start of ABSK061 administration until 7 days after administration of ABSK061. Medications up to 14 days prior to dosing of ABSK061 until the end of dosing will be considered prior and will also be collected.

Table 5 Part II Study Plan (Multiple Doses)

Study Procedures	Screening 1	Baseline	Study Period 2						Follow-up 3	Early Withdrawal 4
	D-14 ~D-2	D-1	D1	D2	D3	D4	D5	D6	D18 (+ 3 days)	
Signed informed consent	×									
Eligibility Criteria	×	×								
Demographic Data 5	×									
Medical history 6	×									
Vital Signs 7	×	×	×	×	×	×	×	×		×
Physical Examination 8	×							×		×
Height and weight 9	×									
Hematology 10	×	×						×		×
Urinalysis 11	×	×						×		×
Blood Chemistry 12	×	×						×		×
Coagulation 13	×	×						×		×
Virology 14	×									
Chest X-ray (anteroposterior) 15	×									
Abdominal ultrasonography (liver, gallbladder, pancreas, spleen, kidney) 16	×									
12-lead ECG 17	×	×	×					×		×
Blood pregnancy test 18	×	×						×		×
Drug abuse screening 19		×								
Alcohol breath screen		×								
Ophthalmic Examination 20	×							×		×
Assign Enrollment Number		×								
Admission to study ward		×								
Taking ABSK06121			×	×	×	×				
PK blood sampling 22			×	×	×	×	×	×		×
Leave study ward								×		×
Telephone follow-up									×	
Adverse Events 23	×									
Prior and concomitant medications 24	×									

Instructions:

1. Screening: all assessments at screening should be completed within 14 days prior to the first dose of investigational product. If screening cannot be completed on time, the sponsor should be contacted to determine if the screening process performed prior to dosing is repeated. All screening examinations must be completed at this site. If a laboratory value at screening does not meet the participant selection criteria, only up to one retest that is judged by the investigator to be required during the screening period is allowed. If the retest value still does not match, the participant should be excluded.
2. Study period: including 4 days of dosing (D1 to D4) and washout from D4 to D6. Participants should be admitted to the clinical study ward of the study site on the day prior to dosing (i.e., D-1), eat uniformly, and undergo relevant visit examinations. Participants cannot leave the clinical study ward of the study site during the trial.
3. Participants should be contacted by telephone follow-up on D18 (+ 3 days) 14 days after the last dose of ABSK061, and information on adverse events and concomitant medications should be collected.
4. Early withdrawal applies to participants who have received at least one dose of ABSK061 and will no longer be followed for safety.
5. Demographic data will include gender, ethnicity, and date of birth of the participant.
6. Medical history inquiry: including past medical history and treatment history, smoking history, alcohol consumption history, drug allergy history, food allergy history, concomitant diseases and treatment. The inquiries are detailed in Protocol 8.3.1 Demographics and Disease History.
7. Vital signs included ear temperature, sitting blood pressure, respiratory rate, and pulse rate. Vital signs are recommended after the participant has rested quietly for at least 5 minutes. Vital signs should be measured at 1 hour (± 1 hour) pre-dose, 2 hours (± 1 hour) post-dose, 6 hours (± 1 hour) post-dose, D5, D6, and at the Early Withdrawal Visit on D1 to D4. Vital signs should be performed prior to PK blood sampling or at least 20 min apart after PK blood sampling. Additional vital sign testing may be added during each study at the discretion of the investigator. If the vital signs test results at screening are not within the normal range, they may be repeated once, and if they are still not within the normal range, the screening fails; participants who have been assigned enrollment numbers may be retested once if their vital signs test results are not within the normal range prior to the first dose on D1, or drop out if they are still outside the normal range and judged by the investigator to be clinically significant.
8. Physical examination: a complete physical examination is required at screening or baseline, and only a general physical examination will be performed during subsequent studies. A complete physical examination included mucocutaneous, lymph nodes, head, neck, chest, abdomen, spine, extremities, and nervous system. General physical examination, which may include head and neck, chest and abdomen, will be determined by the investigator as clinically indicated.
9. Height and weight: collected at Screening or Baseline only. Investigators may perform more frequent tests if clinically indicated.
10. Hematology: including red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT) and total platelet count (PLT), white blood cell count (WBC) with differential and proportion (including neutrophil percentage and absolute neutrophil percentage, lymphocyte percentage and absolute lymphocyte count, monocyte percentage and absolute monocyte count, eosinophil percentage and absolute eosinophil percentage, basophil percentage and absolute basophil percentage). If hematology at screening is performed within 7 days prior to the first dose, hematology will not be performed separately at baseline on D-1.
11. Urinalysis: including specific gravity, glucose, protein, ketones, occult blood, and red blood cells. Participants with significant clinical findings should be further

evaluated. If urinalysis at screening is performed within 7 days prior to the first dose, urinalysis will not be performed separately at baseline on D-1.

12. Blood chemistry: includes total bilirubin, direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), lactate dehydrogenase, glucose, urea, creatinine, total cholesterol, triglycerides, potassium, sodium, chloride, calcium, phosphorus, magnesium, carbon dioxide. In the event of ≥ CT CA E2 transaminase elevations during the trial, more frequent liver function tests (at least twice weekly) will be required until recovery to Grade 1 or baseline. Additional laboratory tests may be performed if clinically indicated. If blood chemistry at screening is performed within 7 days prior to the first dose, blood chemistry will not be performed separately at baseline on D-1.

13. Coagulation: includes prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), plasma fibrinogen (Fbg), and thrombin time (TT). If coagulation at screening is performed within 7 days prior to the first dose, coagulation tests will no longer be performed separately at baseline on D-1.

14. Virology: including five tests for hepatitis B virus (HBV): hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), and hepatitis B core antibody (HBcAb); treponema pallidum antibody, hepatitis C virus antibody (HCV-Ab), human immunodeficiency virus antibody. If virology at screening is performed within 28 days prior to the first dose, virology will no longer be performed separately at Screening and Baseline.

15. Chest X-ray (anteroposterior) will be performed only once at screening or baseline and results within 3 months prior to signing the informed consent form are acceptable.

16. Abdominal B-ultrasound (liver, gallbladder, pancreas, spleen, kidney) will be performed only once at screening or baseline. If abdominal B-ultrasound at screening is performed within 28 days prior to the first dose, abdominal B-ultrasound will not be performed separately at screening and baseline.

17. 12-lead ECG: a 12-lead ECG will be performed once each at screening and at D-1 baseline, D6, and at the Early Withdrawal Visit. If the 12-lead ECG at screening is performed within 7 days prior to the first dose, a 12-lead ECG will not be performed separately at D-1 baseline. In Part II, serial 12-lead ECG measurements were performed at 1 hour (± 15 minutes), 30 minutes (± 15 minutes), and 15 minutes (± 15 minutes) before dosing and 30 minutes (± 15 minutes), 1 hour (± 15 minutes), and 1.5 hours (± 15 minutes) postdose on the first day of dosing (D1). Participants should remain supine or semi-recumbent for at least 10 minutes prior to each ECG examination. Triplicate measurements were performed at each time point ≥ 1 minute apart, and triplicate recordings at each time point should be completed within 10 minutes. A total of 6 12-lead ECGs were required on D1. 12-lead ECGs should be performed prior to invasive tests (e.g., PK blood sampling, etc.). Additional ECGs may be performed by the investigator as clinically indicated. The 12-lead ECG should include heart rate, RR interval, PR interval, QT interval, and calculation of QTcF. The specific examination requirements of 12-lead ECG are detailed in Protocol 8.3.4 12-lead ECG.

18. For female participants of childbearing potential, a blood pregnancy test is required at Screening, D-1 Baseline, D6, and Early Withdrawal Visit. A blood pregnancy test is not required for women of non-childbearing potential. Women of non-childbearing potential were defined as postmenopausal (≥ 12 months postmenopausal) or had a documented bilateral tubal ligation, complete oophorectomy, or hysterectomy. If the blood pregnancy test at screening is performed within 2 days prior to the first dose, the blood pregnancy test will not be repeated at baseline on D-1.

19. The drug screen included morphine, ketamine, methamphetamine, dimethylene dioxyamphetamine, and tetrahydrocannabinol acid.

20. Ophthalmic Examination: participants were evaluated ophthalmologically by an ophthalmologist at Screening, D6, Early Withdrawal Visit. Each ophthalmologic assessment should be performed by the same ophthalmologist whenever possible. Specific examination requirements are detailed in 8.3.7 Ophthalmic Examination.

21. Taking ABSK061: the drug should be taken in a fasted state from D1 to D4. Refer to Section 7.6 for details.

22. The time windows for PK blood sample collection are detailed in Table 8 Part II PK sampling times.

23. Adverse events will begin when the participant signs the informed consent form until 14 days after the last dose of ABSK061 (i.e., D18), as detailed in 8.3.13 Safety Reporting Period.

24. Concomitant medication information was collected from the first dose of ABSK061 until 14 days after the last dose of ABSK061. Medications up to 14 days prior to the first dose of ABSK061 until the end of the first dose will be considered prior and will also be collected.

Table 6 Part III Study Plan

Study Procedures	Screening 1	Baseline	Study Period Period 1 2			Study Period Period 2 3			Study Period Period 3 4			Follow-up 5	Early Withdrawal 6
	D-14 ~D-2	D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D14 (+ 3 days)	
Signed informed consent	×												
Eligibility Criteria	×	×											
Demographic Data7	×												
Medical history 8	×												
Vital Signs 9	×	×	×	×	×	×	×	×	×	×	×		×
Physical Examination 10	×				×			×			×		×
Height and weight 11	×												
Hematology 12	×	×			×			×			×		×
Urinalysis 13	×	×			×			×			×		×
Blood Chemistry 14	×	×			×			×			×		×
Coagulation 15	×	×			×			×			×		×
Virology 16	×												
Chest X-ray (anteroposterior) 17	×												
Abdominal ultrasonography (liver, gallbladder, pancreas, spleen, kidney) 18	×												
12-lead ECG 19	×	×	×		×	×		×	×		×		×
Blood pregnancy test 20	×	×									×		×
Drug abuse screening 21		×											
Alcohol breath screen		×											
Ophthalmic Examination 22	×										×		×
Randomization		×											
Admission to study ward		×											
Taking ABSK06123			×			×			×				
PK blood sampling 24			×	×	×	×	×	×	×	×	×		×
Confirmation of Cycle 2 25					×								
Confirmation of Cycle 3 26								×					
Leave study ward											×		×
Telephone follow-up												×	
Adverse Events 27	×												

Study Procedures	Screening 1	Baseline	Study Period Period 1 2			Study Period Period 2 3			Study Period Period 3 4			Follow-up 5	Early Withdrawal 6
	D-14 ~D-2	D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D14 (+ 3 days)	
Prior and concomitant medications 28	×												

Instructions:

1. Screening: all assessments at screening should be completed within 14 days prior to the first dose of investigational product. If screening cannot be completed on time, the sponsor should be contacted to determine if the screening process performed prior to dosing is repeated. All screening examinations must be completed at this site. If a laboratory value at screening does not meet the participant selection criteria, only up to one retest that is judged by the investigator to be required during the screening period is allowed. If the retest value still does not match, the participant should be excluded.
2. Cycle 1 of the study period: including the administration on Day 1 of Cycle 1 (D1) and the washout from D1 to D3. Participants should be admitted to the clinical study ward of the study site on the day prior to dosing (i.e., D-1), eat uniformly, and undergo relevant visit examinations.
3. Period 2 of the study period: subjects who complete the relevant visit examinations on Day 3 of Cycle 1 (D3) and are judged as eligible by the investigator will conduct the study in Period 2, which includes dosing on D4 and washout from D4 to D6. Participants cannot leave the clinical study ward of the study site during the trial.
4. Cycle 3 of the study period: subjects who complete the relevant visit examinations on Day 3 of Cycle 2 (D6) and are judged as eligible by the investigator will conduct the study in Cycle 3, which includes dosing on D7 and washout from D7 to D9. Participants cannot leave the clinical study ward of the study site during the trial.
5. Should be taken last time Participants were contacted by telephone follow-up 7 days (+ 3 days) after ABSK061 to collect information on adverse events and concomitant medications.
6. Early withdrawal applies to participants who have received at least one dose of ABSK061 and will no longer be followed for safety.
7. Demographic data will include gender, ethnicity, and date of birth of the participant.
8. Medical history inquiry: including past medical history and treatment history, smoking history, alcohol consumption history, drug allergy history, food allergy history, concomitant diseases and treatment. The inquiries are detailed in Protocol 8.3.1 Demographics and Disease History.
9. Vital signs included ear temperature, sitting blood pressure, respiratory rate, and pulse rate. Vital signs are recommended after the participant has rested quietly for at least 5 minutes. Vital signs in each period should be measured at 1 hour (± 1 hour) pre-dose, 2 hours (± 1 hour) post-dose, 6 hours (± 1 hour) post-dose, 24 hours (± 1 hour) post-dose, 48 hours (± 1 hour) post-dose, and at the Early Withdrawal Visit. Vital signs should be measured before or after at least a 20-minute interval after PK blood sampling. Additional vital sign testing may be added during each study at the discretion of the investigator. If the vital signs test results at screening are not within the normal range, they may be repeated once, and if they are still not within the normal range, the screening fails; participants who have been assigned a randomization number may be retested once if the vital signs test results prior to the first dose on D1 of Cycle 1 are not within the normal range or drop out if they are still not within the normal range and are judged by the investigator to be clinically significant.
10. Physical examination: a complete physical examination is required at screening or baseline, and only a general physical examination will be performed during subsequent studies. A complete physical examination included mucocutaneous, lymph nodes, head, neck, chest, abdomen, spine, extremities, and nervous system. General physical examination, which may include head and neck, chest and abdomen, will be determined by the investigator as clinically indicated.

11. Height and weight: collected at Screening or Baseline only. Investigators may perform more frequent tests if clinically indicated.

12. Hematology: including red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT) and total platelet count (PLT), white blood cell count (WBC) with differential and proportion (including neutrophil percentage and absolute neutrophil percentage, lymphocyte percentage and absolute lymphocyte count, monocyte percentage and absolute monocyte count, eosinophil percentage and absolute eosinophil percentage, basophil percentage and absolute basophil percentage). If hematology at screening is performed within 7 days prior to the first dose, hematology will not be performed separately at baseline on D-1.

13. Urinalysis: including specific gravity, glucose, protein, ketones, occult blood, and red blood cells. Participants with significant clinical findings should be further evaluated. If urinalysis at screening is performed within 7 days prior to the first dose, urinalysis will not be performed separately at baseline on D-1.

14. Blood chemistry: includes total bilirubin, direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamyl transpeptidase (GGT), lactate dehydrogenase, glucose, urea, creatinine, total cholesterol, triglycerides, potassium, sodium, chloride, calcium, phosphorus, magnesium, carbon dioxide. In the event of ≥ CTCAE Grade 2 transaminase elevations during the trial, more frequent liver function tests (at least twice weekly) will be required until recovery to Grade 1 or baseline. Additional laboratory tests may be performed if clinically indicated. If blood chemistry at screening is performed within 7 days prior to the first dose, blood chemistry will not be performed separately at baseline on D-1.

15. Coagulation: includes prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), plasma fibrinogen (Fbg), and thrombin time (TT). If coagulation at screening is performed within 7 days prior to the first dose, coagulation tests will no longer be performed separately at baseline on D-1.

16. Virology: including five tests for hepatitis B virus (HBV): hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), and hepatitis B core antibody (HBcAb); treponema pallidum antibody, hepatitis C virus antibody (HCV-Ab), human immunodeficiency virus antibody. If virology at screening is performed within 28 days prior to the first dose, virology will no longer be performed separately at Screening and Baseline.

17. Chest X-ray (anteroposterior) will be performed only once at screening or baseline and results within 3 months prior to signing the informed consent form are acceptable.

18. Abdominal B-ultrasound (liver, gallbladder, pancreas, spleen, kidney) will be performed only once at screening or baseline. If abdominal B-ultrasound at screening is performed within 28 days prior to the first dose, abdominal B-ultrasound will not be performed separately at screening and baseline.

19. 12-lead ECG: a 12-lead ECG will be performed once at screening and once at baseline on D-1. If the 12-lead ECG at screening is performed within 7 days prior to the first dose, 12-lead ECG will not be performed separately at D-1 baseline. A single 12-lead electrocardiogram was performed 1 hour (± 1 hour) before dosing on the day of dosing (D1, D4, D7) of each period, the day of confirming whether to enter the next cycle (D3, D6), the day of leaving the ward (D9), and early withdrawal. The 12-lead ECG before dosing on the day of dosing in each period should be performed before PK blood sampling, and the remaining 12-lead ECGs should be performed at least 45 minutes apart if required after invasive tests (e.g., PK blood sampling, etc.). Additional ECGs may be performed by the investigator as clinically indicated. The 12-lead ECG should include heart rate, RR interval, PR interval, QT interval, and calculation of QTcF. The specific examination requirements of 12-lead ECG are detailed in Protocol 8.3.4 12-lead ECG.

20. For female participants of childbearing potential, a blood pregnancy test is required at Screening, D-1 Baseline, and D9/Early Withdrawal. A blood pregnancy test is not required for women of non-childbearing potential. Women of non-childbearing potential were defined as postmenopausal (≥ 12 months postmenopausal) or had a documented bilateral tubal ligation, complete oophorectomy, or hysterectomy. If the blood pregnancy test at screening is performed within 2 days prior to the first dose, the blood pregnancy test will not be repeated at baseline on D-1.

21. The drug screen included morphine, ketamine, methamphetamine, dimethylene dioxyamphetamine, and tetrahydrocannabinol acid.

22. Ophthalmic Examination: participants were evaluated ophthalmologically by an ophthalmologist. Each ophthalmologic assessment should be performed by the same ophthalmologist whenever possible. Specific examination requirements are detailed in 8.3.7 Ophthalmic Examination.

23. Taking ABSK061: the drug should be taken in a fasted state on the first day of Cycle 1, Cycle 2, and Cycle 3, respectively. Refer to Section 7.6 for details.

24. The time windows for PK blood sample collection are detailed in Table 9 Part III PK sampling times.

25. On Day 3 of Cycle 1 (D3), the investigator will comprehensively determine whether the participant enters the study in Period 2 based on the participant ’ s physical condition and relevant visit test results.

26. On Day 3 of Cycle 2 (D6), the investigator will comprehensively determine whether the participant enters the study in Cycle 3 based on the participant ’ s physical condition and relevant visit test results.

27. Adverse events will begin when the participant signs the informed consent form until 7 days after the last dose of ABSK061 (i.e., D14), as detailed in 8.3.13 Safety Reporting Period.

28. Concomitant medication information was collected from the first dose of ABSK061 until 7 days after the last dose of ABSK061. Medications up to 14 days prior to the first dose of ABSK061 until the end of the first dose will be considered prior and will also be collected.

Sampling Schedule

Table 7Part I PK Sampling Times

Visit / Sampling time (window)	D1	Early Withdrawal 1
Pre-dose (-60 minutes)	×	×
30 minutes (± 5 minutes)	×	
1 hour (± 10 minutes)	×	
1.5 hours (± 10 minutes)	×	
2 hours (± 10 minutes)	×	
4 hours (± 10 minutes)	×	
6 hours (± 15 minutes)	×	
10 hours (± 15 minutes)	×	
24 hours (± 1 hour) 2	×	
48 hours (± 1 hour) 3	×	

Instructions:

1. PK sampling for "early withdrawal" participants should be completed within 24 hours of investigator decision;
2. The PK sampling point of a single dose of Part I at 24 h occurred on D2;
3. The PK sampling point of a single dose of Part I at 48 h occurred on D3;

Table 8Part II PK Sampling Times

Visit / Sampling time (window)	D1	D2	D3	D4	Early Withdrawal 1
Pre-dose (-10 minutes)	×	×	×	×	
30 minutes (± 5 minutes)	×			×	
1 hour (± 10 minutes)	×			×	
1.5 hours (± 10 minutes)	×			×	
2 hours (± 10 minutes)	×			×	×
4 hours (± 10 minutes)	×			×	
6 hours (± 15 minutes)	×			×	
10 hours (± 15 minutes)	×			×	
24 hours (-10 minutes) 2				×	
48 hours (-10 minutes) 2				×	

Instructions:

1. PK sampling for "early withdrawal" participants should be completed within 24 hours of investigator decision;
2. Since there was no dosing schedule on D5 of the MAD study, PK blood sampling at 24 and 48 hours after the last dose on D4 had to be completed within the first 10 minutes of the 24 hour and 48 hour time point after the last dose. If dosing was completed at 8 AM on D4, the corresponding 24 and 48 hour PK sampling times were 7 AM on D5, respectively：50 -8: 00 and D6 7 AM：50 -8 ：00。

Table 9Part III PK Sampling Times

Visit / Sampling time (window)	Cycle 1	Cycle 2	Cycle 3	Early Withdrawal 1
	D1	D4	D7	
Pre-dose (-60 minutes)	×	×	×	
30 minutes (± 5 minutes)	×	×	×	
1 hour (± 10 minutes)	×	×	×	
1.5 hours (± 10 minutes)	×	×	×	
2 hours (± 10 minutes)	×	×	×	×
4 hours (± 10 minutes)	×	×	×	
6 hours (± 15 minutes)	×	×	×	
10 hours (± 15 minutes)	×	×	×	
24 hours (± 1 hour) 2	×	×	×	
48 hours (± 1 hour) 3	×	×	×	

Instructions:

1. PK sampling for "early withdrawal" participants should be completed within 24 hours of investigator decision;
2. PK sampling points at 24 h in Cycle 1, Cycle 2 and Cycle 3 of Part III occurred on D2, D5, and D8, respectively;
3. The 48 h PK sampling points of Part III Cycle 1, Cycle 2 and Cycle 3 occurred on D3, D6, and D9, respectively.

1 Study Background

1.1 Overview of ABSK061

ABSK061 is a new molecular entity developed by Shanghai Hezhu Biopharmaceutical Technology Co., Ltd. It is a selective and potent inhibitor of fibroblast growth factor receptor 2/3 (FGFR2/3) and is effective orally. In vitro and in vivo pharmacology data showed potent and selective inhibition of FGFR2/3 by ABSK061 and demonstrated significant antitumor effects in FGFR2/3-dependent xenograft mouse models. The drug metabolism and pharmacokinetic profile of ABSK061 is favorable for oral administration, and the risk of drug-drug interaction DDIs is expected to be small.

Preclinical study data for ABSK061 support the clinical development of this investigational medicinal product. The toxicity profile of ABSK061 has been confirmed by preclinical safety assessments to support clinical investigation of the investigational product in different tumor types with FGFR2/3 mutations/fusions. Please refer to the Investigator ' s Brochure for more information on preclinical studies.

achondroplasia (ACH) is the most common dwarfism in humans, which belongs to autosomal dominant disease. Mutations in the FGFR3 gene are the main cause of the disease. In recent years, drug development strategies targeting the overactive FGFR3 receptor and downstream signaling have begun to evolve. ABSK061 will also be planned for the development of this pediatric indication.

1.2 Preclinical Study Results

ABSK061 was shown to be moderately to highly permeable in vitro, suggesting that it may be a substrate for efflux transporters. In pharmacokinetic studies in rats and dogs, ABSK061 was moderately cleared and the volume of distribution following intravenous administration was close to or slightly higher than the total volume of body fluids. The absolute bioavailability was 50%, 72% and 72% after a single oral dose in male rats, 72% in female rats, and dogs, respectively. The elimination half-life was 1.2 h in rats and 0.9 h in dogs; cmax and AUClast increased proportionally with increasing dose. Pharmacokinetic and toxicokinetic results of repeated dosing showed no accumulation of ABSK061 in rats and dogs at any dose level for 28 consecutive days.

After administration of ABSK061, its oxidative metabolites could be detected, and there were no species differences in its major metabolic pathways. ABSK061 is mainly metabolized by CYP3A4 enzymes. ABSK061 showed an extensive metabolic profile in rats following oral administration. The major metabolic pathways of ABSK061 were oxidative dehydrogenation, dealkylation, and sulfation.

ABSK061 showed weak inhibitory effects on CYP2C8, CYP2C9, CYP2C19 and moderate inhibition on CYP3A4 (based on midazolam) and CYP3A4 (based on testosterone); no induction of cytochrome P450 enzymes such as CYP1A2, CYP2B6 and CYP3A4 was demonstrated.

Other preclinical study results are detailed in the ABSK061 Investigator ' s Brochure V3.0.

1.3 Clinical Study Results

ABSK061 is currently conducting "An Open-Label Phase 1 Study to Evaluate the Safety, tolerability, and Pharmacokinetics of ABSK061 in Patients with Advanced Solid Tumors"(ABSK061-101). The study consists of a 28-day treatment cycle consisting of a dose escalation phase and an expansion phase to evaluate the safety and tolerability of the drug, as well as preliminary anti-tumor activity. A total of 198 participants are expected to be recruited.

Safety Data

As of 27 September 2024, ABSK061-101 has conducted dose escalation studies in a total of 9 cohorts of 5 mg BID/10 mg BID/20 mg BID/35 mg BID/50 mg BID/75 mg BID/100 mg BID/150 mg QD/200 mg QD, with a total of 47 adult patients with advanced solid tumors enrolled in the study. A total of 47 (47/47, 100.0%) patients experienced at least 1 TEAE, including 4 (4/47, 8.5%) deaths due to TEAEs (all due to disease progression and unrelated to study drug). Drug-related TEAEs of CT CAE Grade ≥ 3 were reported in 6 (6/47, 12.8%) patients and drug-related serious TEAEs were reported in 1 (1/47, 2.1%) patient. Drug-related TEAEs leading to treatment interruption were reported in 16 (16/47, 34%) patients, drug-related TEAEs leading to dose reduction were reported in 8 (8/47, 17%) patients, and no drug-related TEAEs led to treatment discontinuation. TEAEs leading to death were reported in 4 (4/47, 8.5%) patients, none of which were due to drug-related TEAEs.

As of 27 September 2024,Treatment-related adverse events (TRAEs) with frequency ≥ 10% included aspartate aminotransferase increased (16/47, 34.0%), alanine aminotransferase increased (15/47, 31.9%), anemia (13/47, 27.7%), hyperphosphatemia (12/47, 25.5%), diarrhea (11/47, 23.4%), blood alkaline phosphatase increased (9/47, 19.1%), hypoalbuminemia/alopecia/rash (7/47, 14.9%), dry mouth/hypokalemia (6/47, 12.8%), and blood creatinine increased/blood lactate dehydrogenase increased/platelet count decreased/retinal pigment epithelium detachment/dry eye (5/47, 10.6%). Most of these hepatic function-related adverse events were Grade 1-2 and transiently increased, which may be more closely related to their own diseases. The potential for this product to cause severe hepatotoxicity in patients is low. This product had some effect on the patient's blood phosphorus laboratory values, but most were transient and did not require dose interruption. Retinal toxicity is highly relevant to individual patients, but safety is manageable, no serious events have occurred, and its incidence is similar to historical data for similar drugs of the same class.

The above study results showed that ABSK061 was generally safe and well tolerated in patients with low safety risk, supporting further clinical studies.

Efficacy data

As of 27 September 2024, a total of 6 partial responses (PRs) were observed in 23 patients with FGFR2 fusion/amplification/mutation, FGFR3 fusion/mutation, with an objective response rate of 26.1%, of which 4 were confirmed partial responses with a confirmed objective response rate of 17.4%; eight stable disease (SD) and nine progressive disease (PD) were observed with a disease control rate of 60.9%.

Clinical Pharmacology

As of June 30, 2024, in the ongoing first-in-human study of ABSK061-101 in China and the United States, intensive PK sampling was performed in 41 patients, including 5 mg BID, 10 mg BID, 20 mg BID, 35 mg BID, 50 mg BID, 75 mg BID, 100 mg BID, and 150 mg QD,

of which 33 patients had evaluable PK data: ABSK061 was rapidly absorbed after a single dose, with a median tmax interval of 0.5 to 1.5 hours across dose groups; the mean terminal t1/2 values for each dose group ranged from 2.9 to 6.8 hours. The apparent volume of distribution of ABSK061 after oral administration ranged from 93 to 136 L, suggesting extensive distribution in vivo. No significant accumulation was observed after multiple doses, with mean accumulation ratios of 1.2 to 2.2 for AUC across dose groups following QD or BID dosing. The inter-individual differences among ABSK061 participants were small, with coefficients of variation of 20% to 43% and 5% to 42% for Cmax, ss and AUCtau, ss, respectively, after multiple doses.

1.4 Risk/Benefit Assessment

ABSK061 is a potent and selective inhibitor of the FGFR2/3 receptor. As of 27 SEP 2024, there were no important identified risks during the clinical development program. Important potential risks include tongue, bone, eye, thymus, and pancreatic abnormalities.

Based on data from ABSK061-101,Drug-related TEAEs with frequency ≥ 10% were: aspartate aminotransferase increased (16/47, 34.0%), alanine aminotransferase increased (15/47, 31.9%), anemia (13/47, 27.7%), hyperphosphatemia (12/47, 25.5%), diarrhea (11/47, 23.4%), blood alkaline phosphatase increased (9/47, 19.1%), hypoalbuminemia (7/47, 14.9%), alopecia (7/47, 14.9%), rash (7/47, 14.9%), dry mouth (6/47, 12.8%), hypokalaemia (6/47, 12.8%), blood creatinine increased(5/47, 10.6%), blood lactate dehydrogenase increased (5/47, 10.6%), platelet count decreased (5/47, 10.6%), detachment of retinal pigment epithelium (5/47, 10.6%), dry eye (5/47, 10.6%). Since the drug is still being studied in Phase 1, close attention should be paid to possible adverse reactions. In order to reduce the overall risk of participants, an appropriate subject population was included through the inclusion/exclusion criteria, close monitoring measures were established during the trial, the effects of the drug on liver, kidney and gastrointestinal systems were closely observed, a strict pharmacovigilance system was established to effectively handle adverse events, and the safety and rights of participants were safeguarded.

Healthy participants were recruited in this study to evaluate the PK profile of a single oral dose of ABSK061 microchip under fasting conditions and the effect of administration with soft food on the PK of ABSK061. Therefore, participation in this study will not bring clinical benefit to healthy participants. Further information on known and expected benefits, risks, SAEs, and reasonably expected AEs of ABSK061 can be found in the Investigator ’ s Brochure.

2 Study Objectives

2.1 Primary Objective

- Part I: to evaluate the pharmacokinetic (PK) characteristics and safety of a single oral dose of ABSK061 microchip in healthy adult participants;
- Part II: to evaluate the safety, tolerability and PK profile of multiple oral doses of ABSK061 microchips in healthy adult participants;
- Part III: to evaluate the effect of ABSK061 microt 5 mg administered with soft food on the PK profile of ABSK061.

2.2 Secondary Objective

- To assess the safety of ABSK061 microchips taken with soft food in healthy adult participants;
- To explore the dose-exposure proportionality of 1 to 35 mg of ABSK061 microchips in healthy adult participants.

3 Study Endpoints

3.1 Primary endpoint

- Safety and tolerability evaluation indicators, including adverse events (AEs), serious adverse events (SAEs), vital signs, physical examinations, electrocardiograms, laboratory tests, ophthalmic examinations, etc.;
- Main PK parameters of ABSK061 micro-tablets, including maximum observed concentration (Cmax), time to reach maximum observed concentration (tmax), area under the plasma concentration-time curve (AUClast and AUC0- ∞), maximum observed concentration during the steady-state dosing interval (Cmax, ss), minimum observed concentration during the steady-state dosing interval (Cmin, ss), area under the concentration-time curve at steady-state dosing interval (AUCtau, ss), and accumulation index (AR);
- PK parameters, mainly including Cmax, AUC0- ∞, and AUClast, following a single dose of ABSK061 microt administration with or without soft food.

3.2 Secondary endpoints

- Secondary PK parameters of ABSK061: including but not limited to terminal elimination half-life (t1/2), apparent clearance (CL/F), and apparent volume of distribution (Vz/F).

4 Study Design

This study is divided into three parts: Part I, II and III. Part I is a single dose study and Part II is a multiple dose escalation (MAD) study with the primary objective to evaluate the tolerability, safety and PK profile of single or multiple ABSK061 microchips in healthy adult participants. Part III is a three-period, three-sequence crossover study with the primary objective to evaluate the effect of ABSK061 microchips taken with soft food on PK. Part II and Part III will be performed in parallel after completion of Part I.

4.1 Overall design

Part I plans to include 18 participants randomized 1: 1: 1 to Sequences A to C for A parallel single-dose trial. Participants in Sequences A, B, C will receive 1 mg, 10 mg, and 35 mg ABSK061 microchips on the first day (D1), respectively, followed by A 7-day safety

observation period. The preset dosing of Parts II and III may be adjusted based on the results of Part I trials.

Part II plans to include 12 participants, prespecified for MAD trials in Sequences D, E. Participants in Sequence D will receive 5 mg ABSK061 microchips orally once daily from D1 to D4, with a 14-day safety observation period after the end of dosing. If the dose escalation criteria are met (see Section 4.4 Dose Escalation Rules), the 20 mg multiple dose group of Sequence E will be conducted, with the same 4-day QD dosing and 14-day safety observation. The dose of Sequence E may be adjusted based on the results of Sequence D. Other doses may be explored based on the test results.

The study design is shown in Figure 1, Part I & II Study Overall Trial Design.

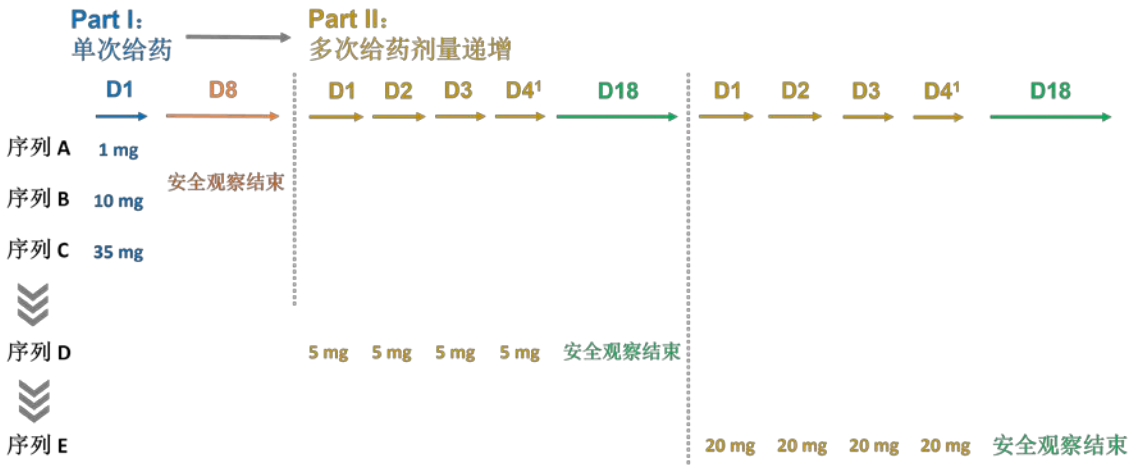

Figure 1 Overall Trial Design of Part I & II Study

Part III plans to include 12 healthy participants randomized 1: 1: 1 to Sequence F, Sequence G, or Sequence H to receive three single doses of Treatment 1, Treatment 2, and Treatment 3. Original pure yogurt (hereinafter referred to as "yogurt", raw milk > 90%, the main ingredients include protein, fat, carbohydrate, sodium, calcium) and applesauce (the main ingredients include carbohydrate and sodium) will be used as two different soft foods to help swallow microchips. Treatment 1 was 5 mg ABSK061 microchip, Treatment 2 was 5 mg ABSK061 microchip taken with a spoon of yogurt (approximately 15 mL), and Treatment 3 was 5 mg ABSK061 microchip taken with a spoon of applesauce (approximately 15 mL). Participants in Sequence F will receive Treatment 1, Treatment 2, and Treatment 3 under fasting conditions in the morning on Cycle 1 Day 1 (D1), Cycle 2 Day 1 (D4), and Cycle 3 Day 1 (D7), respectively; participants in Sequence G will receive Treatment 2, Treatment 3, and Treatment 1 in the morning on D1, D4, and D7, respectively; participants in Sequence H will receive Treatment 3, Treatment 1, and Treatment 2 fasted in the morning on D1, D4, and D7, respectively. All participants were required to drink 180 mL of water immediately after taking the investigational drug or with food. A washout period of 3 days per cycle.

The study design is shown in Figure 2, Part III Study Overall Trial Design.

Figure 2 Overall Trial Design of Part III Study

Pre-dose and post-dose plasma samples were collected from all participants for concentration determination of ABSK061 and its potential high proportion of metabolites, if applicable, and PK assessments were performed.

Drug safety will be assessed by recording adverse events, clinical laboratory tests, and follow-up of vital signs, etc.

Whether or not a participant completing the current period of the study enters the next cycle of the study will be determined comprehensively by the investigator based on the participant's physical condition and relevant visit examination results. For participants who interrupt or permanently discontinue the study due to an adverse event or clinically significant laboratory abnormality, the frequency of visits will be determined comprehensively as required by the Testing Facility or as clinically indicated until the AE resolves or stabilizes, whichever occurs first.

4.2 Scientific Rationale for Study Design

ABSK061 is planned to be used to explore the treatment of ACH in the pediatric population. The formulation was changed from capsules in ABSK061-101 to microcapsulated microparticles given that the target population for treatment was children 3 to 12 years of age and the therapeutic dose was low. Pharmacokinetic experiments with single gavage doses of 25 mg ABSK061 capsules and ABSK061-NX microt in Beagle dogs showed no significant difference in PK behavior between the two formulations, with mean Cmax and AUC0-inf of 1510 ng/mL, 2490 ng · h/mL (ABSK061 capsules), and 1300 ng/mL, 2460 ng · h/mL (ABSK061-NX microt), respectively. In ABSK061-101, there was a linear relationship between drug exposure and dose over a single dose of 35 mg. The effective dose of ABSK061 for ACH is expected to be below the dose-linear range of this investigational drug, where a dose range of 1 mg to 20 mg may cover the majority of the ACH pediatric population. In order to better understand the drug exposure of ABSK061 at low doses and the pharmacokinetic characteristics of microchips, referring to the Technical Guidelines for Clinical Pharmacokinetic Studies of Chemical Drugs issued by the Center for Drug Evaluation of the National Medical Products Administration in March 2005, Part I of this study plans to conduct single-dose pharmacokinetic studies at three doses of 1 mg, 10 mg and 35 mg, and multiple dose escalation PK studies of 5 mg and 20 mg will be conducted in Part II to further explore the safety and tolerability of the study drug.

Based on the ABSK061-101 study, no Grade ≥ 2 drug-related adverse events were reported in any of the 6 patients in the 5 to 35 mg BID dose groups, and the three dose groups (1, 10, 35 mg) of a single dose of Part I will be conducted in parallel with a 7-day safety

observation.

The Part II Multiple Dose Escalation (MAD) study will evaluate the safety and tolerability of ABSK061 at this dose by conducting repeat dose trials of 5 mg and 20 mg successively based on the results of the single dose study. The placebo group will not be included in this study. Since most ABSK061-related TEAEs in ABSK061-101 are abnormalities such as laboratory tests and ophthalmic examinations, relevant monitoring items have been included in this study as the primary and objective evaluation indicators of safety, and whether the placebo group is set up will not have an impact on objective results such as laboratory parameters and PK. The trial was small in size and limited in sample size, and the addition of placebo significantly reduced the efficiency of the trial. Based on the half-life (median 5.4 h in adult oncology patients) and dosing frequency (QD) of the study drug, it can be stable after approximately 3.3 consecutive days of dosing, so it is proposed to test steady-state PK after 4 consecutive days of dosing in this MAD trial. Finally, the safety observation period for this MAD study is proposed to be 14 days due to the short half-life of the investigational drug, which can be completely eluted from the body within 3 days.

The PK of 5 mg ABSK061 was performed in Part III and the effect on the PK of the investigational drug at this dose when the microchip was taken with soft food, since dysphagia may still be present in young children, and 5 mg fell within the effective dose interval for children with ACH at that age based on the estimated effective dose. Common pure yogurt and applesauce 2,3 will be used in this study as soft foods to help swallow. Participants in the control group took the tablets directly with 180 mL of water, and participants in the test group were required to take 180 mL of water immediately after helping swallow the tablets with yogurt or applesauce to evaluate the effect of a soft meal on PK. A washout period of 3 days (more than 7 half-lives) was set between the two doses of the participants, minimizing the potential carryover of the study drug in the previous cycle. The last blood sampling point 48 h after administration also covers 7 half-lives, which can ensure the AUC0- ∞ of the extrapolated drug.

4.3 Rationale for Dose Selection

The doses of ABSK061 in this study were selected as single doses at 1 mg, 10 mg, and 35 mg, multiple dose escalations at 5 mg and 20 mg, and the effect of soft food at 5 mg on PK based on the following reasons:

a. Based on data from Study ABSK061-101, doses of 35 mg and below were safe and well tolerated in patient studies: a total of one participant experienced treatment-related TEAEs (sinus bradycardia, electrocardiogram T-wave abnormality, constipation, proteinuria, all of which were CT CA E Grade 1 in the 10 mg BID dose group); there were no events of drug dose reduction or discontinuation due to any treatment-related TEAEs.

b. The effective dose of ABSK061 for the treatment of ACH is expected to be 0.1 to 0.5 mg/kg, whereas the median weight of children with ACH aged 3 to 12 years is 12 to 31 kg4. For the target population with ACH, doses ranging from 1 to 35 mg are potential therapeutic doses for children with ACH.

c. Given that the PK results in ABSK061-101 show an accumulation index of approximately 2 after repeated dosing of the study drug, single doses (10 mg and 35

mg) of the high dose will be initiated in this study and the Part II dose escalation study will be conducted after the end of the Part I safety observation period, and PK and safety data from Part I can support systemic exposure of 5 mg/20 mg in subsequent multiple dose groups.

4.4 Dose Escalation Rules

The prespecified starting dose in Part II and 5 mg in Part III will be tested in Part II and III by the investigator and the sponsor after adequate assessment of safety data and available PK data for all participants in Part I.

In the Part II multiple dose escalation PK study, interruption of dose escalation will be considered if any of the following occurs in the first dose group (Sequence D). The investigator and sponsor will decide to continue escalation to a preset dose or an intermediate dose (E.g., a dose lower than the preset dose, such as 10 mg or 15 mg) based on safety data and PK data from Sequence D (Sequence E) if the following does not occur:

1. Grade 3 adverse events assessed by the investigator as at least possibly related to ABSK061 in ≥ 2 participants
2. Grade 4 adverse events assessed by the investigator as at least possibly related to ABSK061 in ≥ 1 participant
3. Serious adverse events assessed by the investigator as at least possibly related to ABSK061 in ≥ 1 participant

If any of the above occurred in the second dose group (Sequence E), the investigator discussed with the Sponsor whether to explore a lower dose based on available safety and PK data.

5 Study Population

5.1 Study Sample Size

Part I: 18 healthy participants (6 per sequence) were enrolled;
Part II: enrollment of 12 healthy participants (6 per sequence);
Part III: twelve healthy participants (4/sequence) were enrolled.

5.2 Participant Selection Criteria

5.2.1 Inclusion Criteria

1) Gender: male or female participants, both male and female;
2) Age: 18 to 45 years (including 18 and 45 years);
3) Weight: male participants weigh ≥ 50.0 kg, female participants weigh ≥ 45.0 kg, and body mass index is in the range of 19.0-26.0 kg/m2 (including cut-off value), and body mass index (BMI) = weight (kg)/height 2 (m2);
4) Able to understand and willing to comply with the study procedures, voluntarily participate in this clinical trial and sign the informed consent form before screening;
5) Male or female participants of childbearing potential must agree to use effective methods of contraception during the study and for 6 months after the last dose of investigational product (see Section 5.5 Pregnancy Restrictions for details) and that male participants do not donate sperm during this period; female participants do not donate eggs during this

period and must be non-pregnant, non-lactating female participants, defined as women after conception until termination of pregnancy, and human chorionic gonadotropin (β-HCG) is within the normal range.

5.2.2 Exclusion Criteria

1) History of bacterial, fungal, parasitic, viral (excluding nasopharyngitis), mycobacterial infection, COVID19 infection within 30 days prior to screening;
2) Prolongation of QT interval corrected for heart rate at screening, QTcF > 450 ms (Note: QTc interval corrected by Fridericia ' s formula), or family history of long QT syndrome;
3) Any of the following ophthalmic exclusion criteria:
   - Current or past medical history of retinal pigment epithelial detachment (RPED)/central serous retinopathy (CSR)
   - Previous laser therapy or intraocular injection for macular degeneration
   - Current concomitant or past medical history of age-related macular degeneration
   - Current concomitant or past medical history of retinal vein occlusion (RVO)
   - Current concomitant or past medical history of retinal degenerative disease
   - Diabetic retinopathy with macular edema
   - Current concomitant or past medical history of any other clinically relevant retinal-choroidal defect
   - Any symptoms of acute ophthalmic disease (within 4 weeks prior to the first dose) or active progression
   - Current concomitant keratopathy (eg, keratitis, corneal abrasion, or ulceration) or conjunctivitis
4) Subjects with a history of motor system, neuropsychiatric system, endocrine system, blood circulation system, respiratory system, digestive system, urinary system, reproductive system abnormalities, etc., or existing diseases, which may affect the assessment of study results;
5) Prior history of gastric or intestinal surgery, or surgery affecting drug absorption, distribution, metabolism, excretion (except for appendicitis surgery); or plan to undergo surgery during the study;
6) Donation of blood or massive blood loss (≥ 400 mL) within 3 months prior to screening or during screening (except for female physiological period); those who have received blood transfusion or blood products within 2 months prior to screening;
7) History of drug abuse or positive urine drug screen (morphine, tetrahydrocannabinol acid, methamphetamine, dimethyldioxyamphetamine, ketamine) within the past 5 years;
8) Those who are allergic to drugs, environment or food or to ABSK061 micro-tablets or its excipients [microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, film-coating premix (gastric soluble)]; those who are prone

to allergic symptoms such as rash and urticaria; for Part III: previously known allergy to yogurt and applesauce;

9) Previous chronic consumption of excessive tea, coffee, or caffeinated beverages (defined as ingestion of more than 6 units of caffeine per day, 1 unit of caffeine equivalent to 177 mL of coffee, 355 mL of tea, 355 mL of cola, or 85 grams of chocolate) or who cannot stop drinking any caffeinated beverage during the trial;
10) Those who consumed more than 14 units of alcohol per week (1 unit = 360 mL of beer or 45 mL of spirits containing 40% alcohol or 150 mL of wine), or were unable to abstain from alcohol during the trial, or had an alcohol breath test result > 0 mg/100 mL within 3 months prior to signing the informed consent form;
11) Smoking ≥ 5 cigarettes per day before signing the informed consent form; or cannot stop using any tobacco products during the trial;
12) Those who have taken strong CYP3A4 inhibitors or inducers (including grapefruit juice, grapefruit hybrids, pomegranates, carambola, grapefruit, Seville oranges and fruit juices or other processed products within 14 days prior to screening and during the screening period, as detailed in Appendix 12.1 Strong CYP3A inducers and inhibitors);
13) Those who have special requirements for diet and cannot comply with the unified diet; specific dietary requirements were: (i) only meals provided by the study site during hospitalization, and (ii) avoidance of strong CYP3A4 inhibitors or inducers during the study;
14) Dysphagia, inability to take the investigational product orally;
15) Lactose intolerance (those who have had milk diarrhea);
16) Those who have used any prescription drugs, over-the-counter drugs, Chinese herbal medicines or health products within 14 days prior to the first dose or plan to use them during the study;
17) Those who have received vaccines (including COVID19 vaccine) within 2 months prior to screening, or have planned vaccination throughout the study;
18) Previous participation as a participant in any other ABSK061-related study and has taken any dosage form of ABSK061; those who have participated in other clinical trials and used other clinical investigational drugs or investigational devices within 3 months prior to screening or during screening, or who plan to participate in other clinical trials during this study, or who are not self-participating in clinical trials;
19) Those with a history of needle sickness, blood sickness or intolerance to venipuncture, or difficulty in blood collection;
20) Abnormal physical examination, hematology, blood chemistry, coagulation function, urinalysis, 12-lead electrocardiogram, chest X-ray (anteroposterior), abdominal B-ultrasound, ophthalmic examination and judged by the investigator to be clinically

significant;

21) Vital signs outside the normal range, and the retest is still outside the normal range.
22) Abnormal serum hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody, treponema pallidum antibody test and judged by the investigator to be clinically significant;
23) Personnel involved in the design or implementation of this study project and their immediate family members (e.g., employees of Shanghai Hezhui Biopharmaceutical Technology Co., Ltd., CRO employees, and employees of the study site);
24) Any other factor that, in the opinion of the investigator, is not suitable for enrollment, may affect the compliance of the participant with the protocol, affect the interpretation of the study results, or increase the participant's safety risk, or the participant withdraws from the trial for his/her own reasons.

5.3 Exercise and dietary restrictions

Participants were required to comply with the following restrictions on exercise and diet throughout the study.

5.3.1 Dietary restriction

Participants consumed only meals provided by the study site during their hospitalization.

All participants should be fasted for at least 10 hours during the night before study drug administration, drinking water (except water for drug administration) is prohibited from 1 hour before dosing to 1 hour after dosing, and no food is allowed for 4 hours after dosing. Participants received a standardized diet throughout the study.

5.3.2 Motor restriction

Participants should refrain from strenuous physical activity from one week prior to the first dose and throughout the study.

5.4 Restrictions on beverages, caffeine, alcohol and tobacco

Beverages: grapefruit, pomegranate, carambola, grapefruit, Seville oranges, Seville orange jam, or beverages and products containing these fruits will be prohibited within 14 days prior to the first dose and throughout the study.

Alcohol: participants are prohibited from heavy alcohol consumption (i.e., greater than 14 units of alcohol per week, approximately 360 mL of beer per unit of 1 unit of alcohol or 45 mL of spirits containing 40% alcohol or 150 mL of wine) within 3 months prior to screening and throughout the study, and during admission to the study ward.

Caffeine/Methylxanthine: participants are prohibited from consuming foods and beverages containing caffeine or methylxanthine, such as coffee, tea, cola, energy drinks, and chocolate, from the time of signing the informed consent form until the end of the study (overdose is defined as intake of more than 6 units of caffeine per day, one unit of caffeine equivalent to 177 mL of coffee, 355 mL of tea, 355 mL of cola, or 85 grams of chocolate).

Smoking: smoking or use of nicotine-containing products is prohibited from the time of

signing the informed consent form until the end of the study.

5.5 Pregnancy restriction

No studies have been conducted on possible side effects of ABSK061 in fetuses or infants. Participants may not participate in this study if they are preparing for pregnancy. Male or female participants of childbearing potential who decide to participate in this study must agree to use appropriate contraception from the time of signing the informed consent form until 6 months after the last dose of the investigational product. Appropriate contraceptive measures include vasectomy (male sterilization), use of condoms, use of contraceptive membranes with spermicidal gel (Pure), contraceptive rings, and surgical birth control.

If a participant ' s partner becomes pregnant at any time during the study, or if the participant believes that her partner may become pregnant, the study doctor must be notified immediately.

6 Investigational Medicinal Products, Medication History and Concomitant Medications

6.1 Physical Properties of Investigational Product

The chemical name of this compound (ABSK061-NX) 3- (2,6-dichloro-3,5-dimethoxyphenyl) -1-methyl-7- (1- (2-morpholinethyl) -1H-pyrazol-4-yl) -1,6-naphthyridin-2 (1H) -one is the free base form of ABSK061.

The formulations provided in this study were ABSK061 capsules in the strengths of 0.2 mg/capsule and 5 mg/capsule, the 0.2 mg strength capsule contained 4 ABSK061 micro-tablets containing 0.05 mg active ingredient, and the 5-mg capsule contained 10 ABSK061 micro-tablets containing 0.5 mg active ingredient. Each tablet contains the following inactive pharmaceutical excipients: microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, film-coating premix (gastric soluble, where the 0.05 mg microt film-coating premix is pink and the 0.5 mg microt film-coating premix is white).

6.2 Labeling of Investigational Product

The label of the investigational product will include the sponsor name, protocol number, drug name, drug dosage form, drug batch number, dosage unit, dosage and administration, duration of use, storage conditions, etc., and indicate that the drug is "for clinical trial use only". The labeling of the investigational medicinal product will contain information that complies with applicable regulatory requirements. The investigational product may not be relabeled without prior approval from the sponsor.

In addition, the labeling or labeling of the investigational product should be in accordance with local and national regulations and will not in any way carry any false or misleading statement and will not indicate that the investigational product is safe or effective for the purposes of the study.

6.3 Packaging and Storage of Investigational Medicinal Products

The shells used for the ABSK061 microt are empty hydroxypropylmethylcellulose capsules (Vcaps Plus 0 #, white opaque cap/white opaque body, Sprinkle). The packaging

materials used for microspheres in ABSK061 capsules are high-density polyethylene (HDPE) bottles for oral solid pharmaceutical use, polyolefin functional combination caps for oral solid pharmaceutical use, and high-density polyethylene desiccant tank (1 g/tank) for oral solid pharmaceutical use. Packed in 75 mL HDPE bottle in 30 capsules per bottle, 1 canister of desiccant.

The investigational product should be stored in accordance with the relevant requirements in the drug label.

6.4 **Management, Dispensing and Recovery of Investigational Medicinal Products**

The investigator is responsible for the investigational product at the study site. The investigator should ensure that the investigational product is used in compliance with protocol requirements. The investigator may designate a pharmacist or other appropriate person to be responsible for drug management and dispensing. The warehousing information, inventory quantity, distribution, return to the sponsor (or destruction after approval by the sponsor) of the investigational product should be fully documented and kept at the study site. These records will be used to demonstrate that the participant has obtained sufficient investigational product from the sponsor to be administered at the dose specified in the protocol. Drug records will include date, quantity, batch/serial number, expiration time (if applicable), and participant number. Records will be reconciled by the sponsor or its designee at the time of monitoring, and the sponsor must be notified immediately if a dispensing error or record mismatch is found. All used and unused investigational product (s) should be retained at the study site until the monitor accountability is completed or the sponsor authorizes destruction. All unused or expired investigational products should be returned to the sponsor or its designated third party, or destroyed and documented with the authorization of the sponsor. The relevant procedures of drug application, distribution, storage, accountability and destruction are detailed in the Investigational Drug Management Manual.

6.5 Prior Medications and Concomitant Therapies

Medications that ended 14 days prior to the first dose of ABSK061 to the end before the first dose of ABSK061 were considered prior medications. Medications taken from the first dose of ABSK061 to 7 days after the last dose were considered concomitant medications in the single-dose PK study of Part I and the soft food co-administration study in Part III. In the MAD study of Part II, medications taken from the first dose of ABSK061 to 14 days after the last dose were considered concomitant medications. Any other medication other than the protocol is prohibited from 14 days prior to the first dose until the entire study unless an AE requiring treatment or other sudden illness (including viral respiratory tract infections such as COVID-19) occurs. If treatment of an AE or other disease is required, the investigator is encouraged to discuss it with the sponsor or the clinical study doctor. Any medication considered necessary for the safety and health of the participant may be administered at the discretion of the investigator and documented in the study medical record. All medications (except study drug) and important non-drug therapies received by the participant during the study must be recorded.

7 Study Procedures

7.1 Study flow

Refer to Table 4 Part I study plan, Table 5 Part II study plan, and Table 6 Part III study plan for specific study procedures. Of these, the study schedule describes the contents and specific times of each study plan throughout the study flow, and the sampling schedule describes the time of PK sample collection. Participants may be asked by the investigator to perform additional safety assessments to determine the relationship between the occurrence or duration of the clinical event and the investigational product, as required by clinical practice.

7.2 Participant Registration and Randomization

Participants will be strictly screened and assessed by the investigator. Once the participant ' s eligibility for participation in the clinical study is confirmed, the investigator or his/her designated study personnel will complete the participant registration form.

After signing a written informed compassionate letter and completing the necessary screening assessments, participants in Parts I and III were assigned to different study sequences according to randomization codes and Part II participants entered different study sequences according to the enrollment number. If a participant withdraws from the study, his/her screening number, randomization number, or enrollment number will not be reused. No participant will be enrolled or initiated with the investigational product until the screening number is registered and assigned.

Assignment of Screening Number

The entire study will consist of three study parts, and participants who sign the informed consent form will be assigned a unique screening number in the format of "S + 3 digit sequential number" in the chronological order of signing the informed consent form. For example: screening number S001 represents the first informed consenting participant at the study site, screening number S002 represents the second informed consenting participant at the study site, and so on.

Assignment of Enrollment Number

Participants who are screened successfully in Part II will be sequentially assigned enrollment numbers in the order of screening numbers in the format of "2000 + 3 digits", e.g., enrollment number 2001 indicates the first participant who has successfully entered Part II according to the order of screening numbers, enrollment number 2002 indicates the second participant who has successfully been screened into Part II according to the order of screening numbers, and so on.

Randomization Number Assignment

Part I: participants screened successfully (i.e. those who meet the inclusion criteria and do not meet the exclusion criteria after screening) will be randomized in A 1: 1: 1 ratio to Sequences A, B, and C. According to the Randomization Plan and/or the Randomization Coding Form (provided by Shanghai Hezhui Biopharmaceutical Technology Co., Ltd.), participants will sequentially assign randomization numbers according to the order of screening numbers. Based on the setting of sample size in this protocol, the proposed range of randomization number is: 1001 ~ 1018.

Part III: participants screened successfully (i.e. participants who meet the inclusion criteria

and do not meet the exclusion criteria after screening) will be randomized in a 1: 1: 1 ratio to Sequence F, Sequence G, or Sequence H. According to the Randomization Plan and/or the Randomization Coding Form (provided by Shanghai Hezhui Biopharmaceutical Technology Co., Ltd.), participants will sequentially assign randomization numbers according to the order of screening numbers. Based on the setting of sample size in this protocol, the proposed range of randomization number is: 3001-3012.

Participant Replacement

Participants who have been randomized to Part I and Part III but fail to receive the first dose for any reason will be replaced and the replacement participant will be consistent with the study sequence of the replaced participant. The random number of the replacement participant will be the random number of the replaced participant plus 100. For example, a participant with a random number of 1001 will be replaced with 1101, a participant with a random number of 3002 will be replaced with 3102, and so on.

Participants who have been assigned an enrollment number to Part II but fail to receive the first dose for any reason will be replaced and the replacement participant will be consistent with the study sequence of the replaced participant. The replacement participant enrollment number will be the replacement participant enrollment number plus 100. For example, a participant with an enrollment number of 2001 will be replaced with 2101, and so on.

Participants who have been dosed are not allowed to be replaced.

7.3 Blinding

This study is an open-label study.

7.4 Screening failure

Participants who have signed informed consent but fail to start dosing for any reason will be considered screening failures. The reason for failure to start dosing will be entered in the Screening Inclusion Form and recorded on the eCRF as required by the eCRF completion guidelines.

7.5 Investigational Product Assignment

Part I: participants were screened to meet eligibility criteria and were randomized 1: 1: 1 to receive A single microchip dose of 1 mg, 10 mg, and 35 mg of ABSK061 in Sequences A to C, respectively.

Part II: participants in Sequence D received once daily oral administration of 5 mg ABSK061 microchips for 4 consecutive days; participants in Sequence E received once daily oral administration of 20 mg ABSK061 microchips for 4 consecutive days.

Part III: after screening and meeting the eligibility criteria, participants were randomly assigned 1: 1: 1 to Sequences F, G, and H to receive Treatment 1 (5 mg ABSK061 microchip fasted), Treatment 2 (5 mg oral ABSK061 microchips sprinkled on a spoon of yogurt under fasting conditions), and Treatment 3 (5 mg ABSK061 microchip was sprinkled on a spoon of applesauce under fasted state). Wherein, participants in Sequence F will receive Treatment 1, Treatment 2, and Treatment 3 in the morning on D1 of Cycle 1 Day 1, D4 on Day 1 of Cycle 2, and D7 on Day 1 of Cycle 3, respectively; participants in Sequence G will receive Treatment 2, Treatment 3, and Treatment 1, respectively, on Cycle 1 Day 1 D1, Cycle 2 Day 1 D4, and

Cycle 3 Day 1 D7 in the morning; participants in Sequence H will receive Treatment 3, Treatment 1, and Treatment 2 in the morning on Cycle 1 Day 1 D1, Cycle 2 Day 1 D4, and Cycle 3 Day 1 D7, respectively.

7.6 Investigational Product Administration

The drug was administered under fasting conditions. All participants were fasted overnight for at least 10 hours before dosing, drinking water was prohibited from 1 hour before dosing to 1 hour after dosing, and no food was allowed for 4 hours after dosing. The investigational product must be swallowed completely and cannot be chewed. When the number of microchips is large, dosing may be divided into multiple doses, but participants must complete swallowing of all microchips at the prescribed dose within 3 minutes.

After removal of the ABSK061 capsules, open the cap and pour out the corresponding number of microt: 5 0.2 mg capsules for 1 mg ABSK061, 10 microt for 5 mg ABSK061, 2 5 mg capsules for 10 mg ABSK061, 4 5 mg capsules for 20 mg ABSK061, and 70 microt for 7 5 mg 35 mg ABSK061.

Part I & II: all participants received the corresponding number of microchips directly with 180 mL of water.

Part III: participants receiving Treatment 1 took 10 0.5 mg tablets directly with 180 mL of water; participants receiving Treatment 2 dispersed 10 0.5 mg tablets on 1 tablespoon of yogurt (approximately 15 mL) and swallowed together, followed by 180 mL of water immediately; participants receiving Treatment 3 sprinkled 10 0.5 mg tablets on 1 tablespoon of applesauce (approximately 15 mL) and swallowed them together, followed by 180 mL of water immediately.

7.7 Study Duration

Including screening period (and baseline period), trial period and safety observation period/follow-up period.

Screening + Baseline: 14 days.

Part I: the single dose PK study consisted of a single dose (1 day) and a safety observation period (7 days).

Part II: the multiple-dose escalation PK study included multiple doses (4 days) and a safety observation period (14 days).

Part III consists of three cycles (3 days per cycle for a total of 9 days) and a safety observation period (7 days). Whether or not a participant completing the current period of the study enters the next cycle of the study will be determined comprehensively by the investigator based on the participant's physical condition and relevant visit examination results.

For participants who interrupt or permanently discontinue the study due to an adverse event or clinically significant laboratory abnormality, the frequency of visits will be determined comprehensively as required by the Testing Facility or as clinically indicated until the AE resolves or stabilizes, whichever occurs first.

7.8 Study Compliance

Dosing will be performed under the supervision of the investigator. After administration, the investigator must examine the oral cavity of the participant to ensure that the investigational

product can be swallowed completely and correctly.

7.9 Dose Modification

No dose modifications were allowed during this study.

7.10 Participants lost to follow-up

A participant will be considered lost to follow-up if he/she fails to return for a visit examination multiple times at the scheduled visit time and the site is unable to contact the participant or the participant explicitly refuses to follow-up. The specific criteria for not being able to contact are: telephone calls twice daily (morning and afternoon), unconnected/hung up/shutdown/shutdown/empty for three consecutive days, which will be recorded as lost to follow-up, each time by the notifier.

7.11 Participant Withdrawal

Participants may withdraw voluntarily from the trial at any time without giving reasons and without any penalty or discrimination. The investigator may also ask the participant to withdraw from the study based on the actual clinical situation of the participant. Reasons for discontinuation or withdrawal from the study may include:

- Adverse events;
- Death;
- Protocol violation;
- Lost to follow-up;
- Withdrawal of consent by participants;
- Pregnancy
- Study termination by the sponsor;
- Participants were considered unsuitable for participation in the study by the investigator.

If a participant experiences vomiting within 2 hours of dosing, the investigator may determine whether the participant needs to withdraw from the study early based on the severity of vomiting.

If a participant voluntarily withdraws from the study, an attempt should be made to contact the participant to determine the reason for discontinuation. For any reason, premature withdrawal should complete all study procedures and assessments required for "early withdrawal". All participants who interrupt the study due to an AE will be followed until the AE resolves or stabilizes, as detailed in 8.3.13 Safety Reporting Period.

7.12 Early termination of the study

The investigator or sponsor may choose to terminate the study prematurely if he/she believes there is sufficient reasonable cause. The party discontinuing the study will provide written notice to the investigator or sponsor stating the reason for discontinuation of the study.

7.12.1 Criteria for Study Suspension or Early Termination

Criteria for study suspension or early termination include:

1. New information on the safety of the investigational product indicates a change in the pre-existing risk profile of the investigational medicinal product, resulting in an unacceptable risk to participants participating in the study.
2. A serious GCP violation occurred that seriously affected the achievement of the primary study objectives or jeopardized the safety of participants.
3. The sponsor may suspend or prematurely discontinue the study for reasons unrelated to the study process.

7.12.2 Criteria for Site Suspension or Early Termination

If a site (including the investigator) is found to be in serious violation of GCP, protocol, contractual agreements, or is unable to ensure the proper conduct of the study, the site may be suspended or prematurely terminated.

7.12.3 Procedures for Suspension or Early Termination of the Study

If the sponsor chooses to suspend or terminate the study itself or a study center, the sponsor will provide instructions for specific procedures for study suspension or early termination; during the suspension or termination of the study, applicable sites will follow this procedure for subsequent operations.

7.13 End of study

A participant is considered to have completed the study if he/she has completed all visits to the study, including the last visit or last trial procedure shown in the flowchart. The end of study was defined as the completion of all procedures in the last visit or flowchart for the last participant (including safety telephone follow-up).

8 Study Assessments

8.1 Pharmacokinetic assessment

8.1.1 PK blood sampling

PK blood samples should be collected according to Table 7 Part I PK sampling times, Table 8 Part II PK sampling times, and Table 9 Part III PK sampling times, and plasma samples of all participants in this study before and after dosing to determine the concentrations of ABSK061 and its metabolites (if applicable) for PK assessment. The actual date and time of each sampling (24-hour clock) will be recorded. The consumables used for blood sample collection are provided in the Laboratory Manual.

8.1.2 Sample analysis

Approximately 2 mL of venous blood samples will be collected at each sampling time point to determine plasma concentrations of ABSK061 and its potential high proportion of metabolites, if applicable.

8.1.3 Sample Handling, Storage and Shipment

PK samples will be analyzed at a central laboratory and plasma sample processing, storage,

labeling, and shipping details will be referenced in a separate laboratory manual.

8.1.4 PK Parameter Analysis

The PK parameters of ABSK061 for each participant under different dosing conditions will be calculated and subjected to descriptive statistical analysis based on individual pharmacokinetic time-concentration profiles and actual sampling times.

The following PK parameters will be reported. Additional PK parameters will be reported if needed.

Table 10 PK parameters and their calculations

	Parameters	**Definition**
Single dose	tmax	Time to peak, i.e. the actual sampling time to reach the peak concentration
	Cmax	Peak concentration, i.e. observed peak concentration
	tlast	Actual time of last quantifiable observed concentration (non-BQL)
	AUClast	Area under the ABSK061 plasma concentration-time curve from 0 to the last measurable (non-BQL) concentration time point (calculated using the Linear Up Log Down trapezoidal method)
	AUC0-∞	The area under the ABSK061 drug concentration-time curve from time 0 to infinity was calculated as follows: AUC0- ∞ = AUClast + Clast/λz; Clast refers to the actual last measurable (non-BQL) plasma concentration of ABSK061.
	kel	Terminal elimination rate constant, calculated by linear regression after logarithmic transformation from the end of the drug concentration-time curve.
	t1/2	Apparent elimination half-life, calculated as follows: t1/2, λ = ln2/λz,
	CL/F	Total apparent clearance of drug after single oral administration: CL/F = Dose/AUC0- ∞
	Vz/F	Apparent volume of distribution of the drug after single oral administration: Vz/F = Dose/(AUC0- ∞ · λz)
Multiple dose	tmax,ss	Actual time of maximum observed concentration during the dosing interval at steady state
	Cmax,ss	Maximum concentration during the dosing interval at steady state
	Cmin,ss	Trough concentrations over the dosing interval at steady state
	AUCtau,ss	Area of the concentration-time curve over the dosing interval at steady state
	ARAUC	Accumulation index based on AUC calculation as follows: ARAUC = AUCtau, ss/AUCtau, sd
	ARCmax	When AUC is not available, the accumulation index will be calculated as Cmax instead of AUC. The accumulation index based on Cmax was calculated as follows: ARcmax = Cmax, ss/Cmax, sd
	t1/2,eff	Effective half-life, calculated as follows: t1/2, eff = Ln (2) * tau/Ln ((AR/(AR-1))), where AR is ARAUC
	CLss/F	CLss/F = Dose/AUCtau,ss

8.2 Pharmacodynamic assessment

This section does not apply to this study.

8.3 Safety assessment

The safety of ABSK061 will be evaluated during the trial by recording adverse events, laboratory tests, vital signs, electrocardiograms, and physical examinations. During the study, the symptoms and signs of the participants after administration should be closely observed. Adverse events or adverse drug reactions should be handled promptly and effectively to ensure

the safety and rights and interests of participants. The type, symptoms, time of onset, degree (or grade), symptomatic treatment and outcome of adverse events should be recorded, and then the adverse events should be analyzed, assessed and statistically analyzed.

8.3.1 Demographic and Disease History

Demographic and medical history information will be collected for all participants at the times indicated in Table 4 Part I study plan, Table 5 Part II study plan, and Table 6 Part III study plan. Demographic information will include participant gender, ethnicity, and date of birth.

Participants will be carefully asked about past medical history and treatment information, food allergy, drug allergy, concomitant diseases and treatments, and smoking and alcohol consumption during the screening period. Past medical history and concomitant diseases should record the disease name, time of onset and drug use in detail; history of drug and food allergy should document drug or food name and allergy symptoms.

8.3.2 Vital signs

For each participant, vital signs including ear temperature, sitting blood pressure, respiratory rate, and pulse rate will be measured according to Table 4 Part I study plan, Table 5 Part II study plan, and Table 6 Part III study plan. Vital signs are recommended after the participant has rested quietly for at least 5 minutes. Vital signs should be performed prior to PK blood sampling or at least 20 min apart after PK blood sampling. Additional vital sign testing may be added during each study at the discretion of the investigator. If the vital signs test results at screening are not within the normal range, they may be repeated once, and if they are still not within the normal range, the screening fails; participants who have been assigned a randomization number/enrollment number may be retested once if the vital signs test results before the first dose on D1 are not within the normal range, or drop out if they remain within the normal range and are judged by the investigator to be clinically significant.

Normal Vital Sign Range:

- 35.9 °C ≤ ear temperature ≤ 37.5 °C
- 90 mmHg ≤ systolic blood pressure < 140 mmHg, 60 mmHg ≤ diastolic blood pressure < 90 mmHg
- 12 beats/min ≤ respiratory rate ≤ 22 beats/min
- 55 beats/min ≤ pulse rate ≤ 100 beats/min

Additional vital sign assessments may be added at scheduled visit timepoints as clinically indicated. Additional orthostatic vital sign assessments should be performed for any AE associated with dizziness, an AE in which differences in body posture may cause symptoms. If an upright measurement is required, the participant should stand for at least 3 minutes first. If the participant feels unable to stand, only supine vital signs will be recorded.

8.3.3 Physical examination, height and weight

The physical examination, which includes a complete physical examination at screening and a general physical examination during the subsequent study, will be performed at the times indicated in Table 4 Part I study plan, Table 5 Part II study plan, and Table 6 Part III study plan. A complete physical examination including mucocutaneous, lymph nodes, head, neck, chest, abdomen, spine, extremities, and nervous system will be performed at screening. General physical examination, which may include head and neck, chest and abdomen, will be determined by the investigator as clinically indicated. Height and weight were collected only

during the screening examination period. Investigators may perform more frequent tests if clinically indicated.

8.3.4 12-lead ECG

The 12-lead ECG will be measured according to Table 4 Part I study plan, Table 5 Part II study plan, and Table 6 Part III study plan.

A 12-lead ECG will be performed once at screening and once at baseline on D-1. If the 12-lead ECG at screening is performed within 7 days prior to the first dose, 12-lead ECG will not be performed separately at baseline on D-1.

The single-dose PK study of Part I will undergo a single 12-lead ECG 1 hour (± 1 hour) before dosing on the day of dosing (D1), the day of leaving the ward (D3), at the safety follow-up visit, and early withdrawal.

A total of 6 12-lead electrocardiograms were required on the day of dosing in the multiple dose escalation PK study of Part II. Serial 12-lead electrocardiograms were performed at 1 hour, 30 minutes, and 15 minutes before dosing on the day of dosing (D1), and at 30 minutes, 1 hour, and 1.5 hours after dosing, with a window of 15 minutes before and after the selected time point. Participants in Part II should remain supine or semi-recumbent for at least 10 minutes prior to each ECG collection. Recordings were performed in triplicate at each time point, at least 1 minute apart, and ECG collection at that time point was completed within 10 minutes. ECG collection for all participants in Part II must be completed prior to PK sampling.

Part III will perform a single 12-lead ECG 1 hour (± 1 hour) prior to dosing on the day of dosing (D1, D4, and D7) of each period, on the day of confirming whether to enter the next cycle (D3 and D6), on the day of leaving the ward (D9), and on the day of early withdrawal.

The 12-lead ECG should include heart rate, RR interval, PR interval, QT interval, and calculation of QTcF. Additional ECGs may be performed by the investigator as clinically indicated.

All ECGs are recommended after the participant has rested quietly for at least 5 minutes. Keep supine and awake during ECG collection. A 12-lead electrocardiogram prior to dosing on the day of dosing should be performed prior to PK blood sampling. In studies in Parts I and III, at least 45 minutes apart is required if the test is performed after an invasive test (e.g., PK blood sampling, etc.).

All abnormal ECGs should be identified as clinically significant by the investigator or designee. The number of examinations may be increased for safety purposes. If a clinically significant abnormal ECG is found after enrollment, the investigator will determine whether the participant can continue the study and confirm whether it is recorded as an adverse event based on 8.3.8 Adverse Events.

8.3.5 Blood pregnancy test

For female participants of childbearing potential, blood pregnancy tests will be performed according to Table 4 Part I study plan, Table 5 Part II study plan, and Table 6 Part III study plan (if blood pregnancy test during the screening examination is performed within 2 days prior to the first dose, blood pregnancy test will not be repeated at baseline on D-1). Blood pregnancy tests are not required for women of non-childbearing potential, defined as postmenopausal (≥ 12 months postmenopausal) or documented bilateral tubal ligation, complete oophorectomy, or hysterectomy.

8.3.6 Laboratory tests

For each laboratory test, it should be performed according to Table 4 Part I study plan, Table 5 Part II study plan, and Table 6 Part III study plan and analytical testing should be completed at the study site. Additional laboratory tests may be performed if clinically indicated.

Laboratory Tests

<table>
<tr><td>Hematology:
Red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT) and total platelet count (PLT), white blood cell count (WBC) with differential and proportion (including neutrophil percentage and absolute neutrophil count, lymphocyte percentage and absolute lymphocyte count, monocyte percentage and absolute monocyte count, eosinophil percentage and absolute eosinophil percentage, basophil percentage and absolute basophil percentage and absolute basophil count)</td><td>Urinalysis:
Specific gravity, glucose, protein, ketones, occult blood and erythrocytes</td><td rowspan="2">Blood chemistry:
Total bilirubin, direct bilirubin, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamine transpeptidase (GGT), lactate dehydrogenase, glucose, urea, creatinine, total cholesterol, triglycerides, potassium, sodium, chloride, calcium, phosphorus, magnesium, carbon dioxide</td><td>Infectious Disease Screening:
Five tests for hepatitis B virus (HBV): hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb) and hepatitis B core antibody (HBcAb); treponema pallidum antibody, hepatitis C virus antibody (HCV-Ab), human immunodeficiency virus antibody</td></tr>
<tr><td>Coagulation:
Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), plasma fibrinogen (Fbg), and thrombin time (TT)</td><td>Drug abuse screening:
Morphine, ketamine, methamphetamine, dimethyldioxyamphetamine, and tetrahydrocannabinol acid</td><td>Pregnancy test:
Blood pregnancy

Alcohol Screening:
Alcohol breath test</td></tr>
</table>

8.3.7 Ophthalmic examination

Participants were evaluated ophthalmologically by an ophthalmologist as indicated in Table 4 Part I study plan, Table 5 Part II study plan, and Table 6 Part III study plan. Each ophthalmologic assessment should be performed by the same ophthalmologist whenever possible.

The following assessments will be performed:

- Visual acuity assessments (best corrected), including near and far vision, were performed separately for each eye
- Slit lamp inspection according to local practice
- Intraocular pressure and ophthalmoscopy
- Optical coherence tomography (OCT) of the macular area of both eyes should be performed at each ophthalmic examination and should be performed once in the event of any clinical symptoms or signs suggestive of RPED. Sites should retain duplicate OCT scans. If OCTs are not included in local clinical practice, similar alternative diagnostic methods should be used to screen for RPED
- Add additional tests as clinically indicated as needed

At any other time, participants will undergo a full ophthalmic assessment if abnormal visual symptoms or signs occur.

8.3.8 Adverse Events

An adverse event (AE) is any untoward medical occurrence that occurs in a patient or clinical study participant that is temporally related to the study intervention. It is not necessarily causally related to the study intervention. Adverse events may include, but are not limited to, the following:

1) worsening of the original (before entering the clinical trial) medical condition/disease (including symptoms, signs, laboratory abnormalities and/or increased frequency);

2) Any new adverse medical condition (including symptoms, signs, newly diagnosed diseases);

3) Abnormal and clinically significant laboratory test results (e.g., blood biochemistry, urinalysis) or other tests (e.g., radiological examination, electrocardiogram, vital signs), including those that worsen from baseline and are considered clinically significant according to the investigator's medical and scientific judgment.

The following are not considered adverse events:

Clinically significant laboratory variables or test abnormalities related to the underlying disease are not considered adverse events unless judged by the investigator to be more severe than expected.

Abnormal Laboratory Findings:

Not all abnormal laboratory results were consistent with adverse events. However, abnormal laboratory results must be reported as adverse events if any of the following criteria are met:

- With symptoms;
- Requires clinical intervention or further investigation or additional diagnostic tests;
- Leading to drug dose modification or discontinuation of study intervention.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormal laboratory test itself should be recorded as an adverse event. If laboratory abnormalities can be described by more precise clinical terms according to standard definitions, clinical terms should be recorded as adverse events.

8.3.9 Serious Adverse Events

A serious adverse event (SAE) is an adverse event occurring at any dose that meets any of the following conditions, regardless of causality:

- Leading to death.
- Life-threatening. Life-threatening refers to an event in which the participant was immediately at risk of death at the time of the event, i.e., excluding an event that hypothetically might have caused death if the event was more severe.
- Requires participant hospitalization or prolongation of hospitalization. A planned hospitalization and/or surgery prior to enrollment of a participant in the study will not be considered an adverse event provided there is no unexpected worsening during the study (e.g., surgery performed earlier than scheduled). Hospitalization for sociality and/or convenience without an untoward medical occurrence is not an adverse event.
- Resulting in permanent or severe disability/incapacity.
- Congenital anomaly/birth defect.

- Important medical event. Important medical events are those that may not result in death or be life-threatening or require hospitalization, but may jeopardize the participant or may require medical or surgical intervention to prevent the occurrence of any of the outcomes listed in the definition of an SAE, based on appropriate medical judgment, which are also considered SAEs. Such medical events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood cachexia or convulsions that do not require hospitalization, or development of drug dependence or drug abuse.

8.3.10 Suspected unexpected serious adverse reaction

Suspected unexpected serious adverse reaction (SUSAR) refers to a suspected and unexpected serious adverse reaction in which the nature and severity of the clinical manifestation exceeds the available information such as the Investigator's Brochure of the investigational Product, the package insert of a marketed drug, or a summary of product characteristics.

8.3.11 Criteria for Severity of Adverse Events

The investigator will assess the severity of AEs according to the toxicity grades described in the Common Adverse Event Evaluation Criteria NCI-CT CA E 5.0. For AEs not listed in CT CA E 5.0, the following standard grades may be used:

Grade 1: mild; asymptomatic or mild; clinical or diagnostic findings only; no treatment required.

Grade 2: moderate; requires small, local, or noninvasive treatment; age-appropriate instrumental activities of daily living (ADL) limitation *.

Grade 3: serious or medically significant but not immediately life-threatening; resulting in hospitalization or prolongation of hospitalization; disabling; self-Rational ADL Limited * *.

Grade 4: life-threatening; urgent treatment is required.

Grade 5: deaths related to AEs.

** Instrumental ADLs refer to cooking, shopping for clothing, using the telephone, managing money, etc.*

** * Self-care ADL refers to bathing, dressing and undressing, eating, washing, taking medications, etc., and not bedridden.*

8.3.12 Criteria for Relationship between Adverse Events and Study Drug

The investigator is obligated to make a medical judgment as to the causal relationship between each AE/SAE and the study intervention.

Investigators should consider and investigate other possible etiologies, temporal associations, and use clinical judgment to determine causality. The investigator will determine the relationship to study drug using the following criteria:

Definitely related:	Events or laboratory abnormalities with a reasonable temporal relationship to drug intake; cannot be explained by disease or other drugs; reasonable response after discontinuation (pharmacology, pathology); events identified from a pharmacological or phenomenological perspective (i.e., objective and specific medical conditions or recognized pharmacological phenomena); rechallenge results (if necessary) passed.
Probably related:	Events or laboratory abnormalities with a reasonable temporal relationship to drug intake; not likely attributable to disease or other drugs; reasonable clinical response after discontinuation; rechallenge testing is not required.

Possibly related:	Events or laboratory abnormalities with a reasonable temporal relationship to drug intake; it can also be explained by disease or other drugs; discontinuation information may be missing or equivocal.
Unlikely related:	Events or laboratory abnormalities that are unlikely (but not impossible) temporally related to drug intake; the disease or other medication may provide a reasonable explanation.
Not related:	The adverse event was not related to study drug. There is no or little likelihood that the study drug causes an adverse event; other conditions, including intercurrent illness, progression or presentation of the condition condition, or response to concomitant medications, provided a good explanation for the event.

For safety reporting purposes, in general, all adverse events classified as "definitely related", "probably related" or "possibly related" will be considered treatment related, and adverse events "unlikely related" and "unrelated" will be considered as treatment-unrelated unless specifically specified by the local drug regulatory authority.

The investigator must make a causality determination for each adverse event before reporting to the sponsor, even if the investigator has limited information in the initial report.

The investigator may change the causality determination based on the information obtained at follow-up and update the causality determination in the follow-up report.

8.3.13 Safety Reporting Period

The reporting period for adverse events in this study begins with the signing of informed consent by the participant (prior to any study-related procedures and/or receipt of study drug) until the last Safety Follow-up Visit (7 days after the last dose of the investigational product in Parts I and III; 14 days after the last dose of the investigational product in Part II). Any serious adverse event occurring after the reporting period must also be reported immediately if a causal relationship to the study drug is suspected.

If a participant fails due to laboratory abnormalities, no AEs will be recorded; however, if an SAE or AE possibly related to the study procedure is screened, the corresponding AE/SAE should be recorded. No AE/SAE is required to be recorded after screening failure, i.e., "AE/SAE report is terminated when screening failure status is determined".

If a participant withdraws from the study and withdraws informed consent for future information collection, the AE/SAE reporting period is terminated at the time of withdrawal of consent.

8.3.14 Reporting Process for AEs and SAEs

Each participant must be carefully monitored for any adverse events. This information should be obtained in the form of non-leading questions (e.g., "How do you feel?"), as well as from signs and symptoms detected during each examination, observations by researchers, and spontaneous reports from participants.

All AEs (serious and nonserious) reported spontaneously by the participant and/or determined by answering open-label questions raised by the study personnel or by observation, physical examination, or other diagnostic procedures must be recorded. Whenever possible, signs and symptoms with common pathological features should be considered a composite event. Concomitant signs or symptoms (eg, abnormal laboratory values) should not be reported as additional adverse events. If the diagnosis is unknown, one or more symptoms may be

reported as separate adverse events. If the subsequently reported symptom is confirmed, the reported symptom term must be modified to "attributable" or "due to" the diagnosis.

All adverse events should be followed until resolution, stable disease, or until the investigator decides that follow-up is not required. After the safety reporting period, AEs determined to be unrelated to the investigational product will no longer be followed up.

For all SAEs occurring during the reporting period, whether initial or follow-up, regardless of causality, the investigator must report the SAE to the sponsor within 24 hours of awareness. SAEs must be followed until resolution, stable disease, or until the investigator decides that follow-up is not required. For study analysis, if the event is not resolved by the end of the study reporting period, it must be recorded as ongoing (not recovered/resolving). For regulatory safety monitoring purposes, a follow-up report should be sent as soon as more information becomes available.

The follow-up report should contain sufficient information required for a complete medical assessment and independent causality determination. All relevant information, such as concomitant medications and disease information, must be provided. For fatal cases, available summaries of necropsy or other death examinations must be submitted as soon as possible.

SAE initial and follow-up reports were submitted via email (contact details below).

All SAEs must be reported regardless of whether or not considered causally related to study drug. The sponsor may request the investigator to provide follow-up information on SAEs.

Contact Information	Sponsor Email: drugsafety@abbisko.com

In the event of a suspected unexpected serious adverse reaction (SUSAR), the sponsor or its authorized representative will comply with the requirements of local regulatory authorities to ensure that the relevant regulatory authorities and all personnel involved in the study are notified as soon as possible. In accordance with local regulations and institutional policies, ethics committees (ECs)/institutional review boards (IRBs) and hospital facilities need to be notified of SUSARs or other required information.

8.3.15 Pregnancy Exposure

Participants are obligated to inform the investigator of any pregnancy that occurs during study treatment and up to 6 months after the last dose of study drug. Pregnancies occurring 6 months after the last dose of study drug or due to sperm donation/sperm preservation prior to study drug exposure are not reported.

Female participants who become pregnant during the clinical trial must immediately discontinue study drug and complete the Early Withdrawal Visit and the Safety Follow-up Visit. If the female partner of a male participant becomes pregnant during the study, the participant must immediately notify the investigator, and the male participant may continue the clinical study. Male participants must commit to use an acceptable method of contraception (to avoid or prevent fetal exposure to study drug) for the duration of the study until 6 months after the last dose of study drug. The investigator must notify the sponsor within 1 working day of becoming aware of the pregnancy of the participant (or his/her partner).

The participant or his/her spouse must be followed up until the end of pregnancy and the infant must be followed up to 1 month of birth, if informed consent is available. A separate

informed consent form (ICF) must be provided to explain these follow-up behaviors. Infant deaths after 1 month of life should also be reported as SAEs if assessed by the investigator as possibly related to study drug exposure. Pregnancy per se does not constitute an AE. Any adverse pregnancy outcome, such as stillbirth, spontaneous abortion, fetal malformation, is considered an SAE and needs to be reported as required for an SAE. The SAE Report Form and Pregnancy Report Form need to be completed separately for the same time limit as the SAE.

8.3.16 Death

All deaths occurring during the adverse event reporting period, whether related to study treatment or not, must be immediately reported to the sponsor as SAEs.

Deaths considered related to this study drug outside of the safety reporting period are required to be reported as SAEs.

8.4 Overdose

Any ABSK061 above the indicated dose will be considered an overdose. There is no specific antidote for ABSK061 and in the event of an overdose, participants should receive appropriate supportive care and record any AEs.

9 Statistical Methods

9.1 Sample Size Estimation

The objective of this study was to evaluate the PK profile of ABSK061 capsules in single or multiple oral doses, to assess the effect of soft food on the pharmacokinetics of ABSK061, and to explore the dose-exposure proportionality of ABSK061 microt. The sample size was estimated based on actual considerations and feasibility, and no hypothesis testing was performed.

The study was planned to enroll 18 participants in Part I and to be randomized in A 1: 1: 1 ratio to three different study sequences, A, B, and C.

Part II plans to enroll 12 participants and preset 2 study sequences (sequences D and E, 6/sequence).

Part III planned to enroll 12 participants and were randomized in a 1: 1: 1 ratio to three different study sequences: F, G, and H. Based on the data from the Phase 1 trial in patients with solid tumors of ABSK061-101, the weighted mean of the geometric coefficient of variation (CVw%) of each dose group was obtained for AUC0- ∞, AUClast and Cmax. Considering that this was the inter-patient coefficient of variation, the intra-individual coefficient of variation (CVw%) in healthy participants in this study was estimated as 70% of the above-mentioned weighted mean, I.e. 27.272%, 27.384%, 21.966%. Although the sample size for this trial is not based on statistical testing, as a reference, it is assumed that there is no difference between the drug taken with water and with soft food. The two-sided 90% confidence intervals for the estimated precision (90% confidence interval half-width) and the Ratio of the Geometric Means Ratio (GMR) of the log-transformed PK parameters (taken with soft food-water) at different sample sizes are presented below.

Table of Estimated Accuracy of Primary PK Parameters at Different Sample Sizes (GMR =

1)

Part III Three-sequence, three-period crossover design	AUC0-∞		AUClast		Cmax	
Evaluable Participants	Accuracy	GMR 90% confidence interval	Accuracy	GMR 90% confidence interval	Accuracy	GMR 90% confidence interval
9	0.222	0.801, 1.249	0.223	0.800, 1.250	0.180	0.835, 1.198
12	0.189	0.828, 1.208	0.189	0.828, 1.208	0.153	0.858, 1.165
15	0.167	0.846, 1.182	0.167	0.846, 1.182	0.135	0.874, 1.145

9.2 **Dataset**

The Screening Analysis Set includes all participants who signed informed consent. For participant disposition summaries and listings only.

The PK Concentration Analysis Set (PCS) includes all participants who have received at least one dose of ABSK061 in capsules and are able to provide at least one evaluable postdose PK blood sample. It will be the primary analysis set for all PK concentration data analyses.

The PK Parameters Analysis Set (PPS) includes all participants who are included in the PK concentration Analysis Set and have at least one PK parameter available for Analysis. It will be the primary analysis set for data analysis of all PK parameters.

The Safety Analysis Set (SST) includes all participants who received at least one dose of ABSK061 in capsules. Summary statistics and/or listings will be performed by treatment group actually received by the participant, primarily for safety analysis.

9.3 **Statistical Analysis Methods**

The statistical analysis of this study will be the responsibility of Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. or its designee. Where applicable, data will be listed and summarized in accordance with Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. or designee reporting criteria. Full details will be documented in the Statistical Analysis Plan (SAP).

9.3.1 General Methods

Descriptive statistics (mean, standard deviation, median, minimum, maximum) will be performed for continuous variables. Frequency distributions and percentages will be summarized for discrete variables. All available data will be included in the data listings.

Specific analyses of all endpoints will be detailed in the Statistical Analysis Plan (SAP).

9.3.2 Participant Disposition

Descriptive statistical analyses will be performed on the number of participants enrolled, received with study drug, reason for discontinuation by study sequence and overall, and the date and reason for discontinuation will be presented at the individual participant level.

9.3.3 Demographic and Baseline Characteristics

Demographic and other baseline data will be summarized descriptively by study sequence and overall based on the Safety Analysis Set.

9.3.4 Administration (study treatment, concomitant therapy, compliance)

All information related to drug management will be listed. Concomitant medications and important non-drug therapies prior to and after administration of study drug ABSK061 will be listed using the Safety Analysis Set.

9.3.5 PK Data Analysis

ABSK061 pharmacokinetic parameters will be calculated and analyzed by a standard noncompartmental model. The PK profile of single or multiple oral doses of ABSK061 microt was assessed based on the primary pharmacokinetic parameters obtained.

Results of PK parameters and summary data will be provided for each participant. Descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation) were calculated for all PK parameters of oral ABSK061 in each treatment group except for tmax, which will be summarized as median, minimum, and maximum. Data listings for all PK parameters will be provided.

Part III assessed the effect of coadministration with soft food on the PK profile of ABSK061. The main PK parameters (Cmax, AUC0- ∞, AUClast) were log-transformed and statistically analyzed using a linear mixed-effects model. The dosing sequence and period in the model served as fixed effects and participants (in sequence) served as random effects. The magnitude of the difference between the Least Squares Means (and their 90% confidence intervals and the Ratio of the Geometric Least Squares Means (RGLSM, taken with soft food/water) and their 90% confidence intervals were estimated by logarithmic transformation, and the intra-individual coefficient of variation was calculated for each parameter.

In addition, the dose-exposure proportionality of ABSK061 microchips was explored by graphical presentation of different doses by primary PK parameters (Cmax, AUC0- ∞, AUClast) and/or dose-normalized primary PK parameters for each treatment group. If applicable, the dose-exposure proportionality will be further explored through the Power model by natural log-transformation of the primary PK parameters.

The detailed analysis plan will be further described in the Statistical Analysis Plan (SAP).

9.3.6 Safety Analysis

Adverse events, clinical laboratory data, vital signs, and electrocardiograms will be assessed using the Safety Analysis Set, with descriptive statistical analysis as the main. Missing safety data will not generally be imputed unless otherwise specified.

9.3.7 Adverse Events

Adverse events occurring in each participant were coded by system organ class and MedDRA preferred term in the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent AEs, TEAEs (new or pre-dose but worsening after the first dose to the last safety follow-up visit) will be summarized. All adverse events, study drug-related adverse events, serious adverse events (SAEs), and adverse events leading to death will be listed.

9.3.8 Laboratory abnormalities

Laboratory measurements and changes from baseline will be summarized descriptively

(mean, median, standard deviation, maximum, minimum) by treatment group. Listings with abnormal values will be provided.

The results of hematology, blood chemistry, urinalysis, and clinical significance as judged by the investigator included in the CRF will be summarized according to the scheduled visit. The number and percentage of participants with measurements judged high, low, or normal compared to the normal laboratory range will be summarized by treatment group using a crossover table, if applicable.

9.3.9 Other safety data

Data from other tests (e.g., electrocardiograms or vital signs) will be listed and flagged with abnormal values. Summary tables of additional safety data will also be provided.

9.3.10 Interim Analysis

Not applicable for this study.

10 Study Management

10.1 Good Clinical Practice

This study will be conducted in strict compliance with the regulatory requirements of ICH-GCP. The investigator needs to be fully familiar with the protocol and the rational use of the investigational product. Necessary clinical documents will be retained to demonstrate compliance with the study and the reliability of the data. Study main body documents should be established at the start of the study and maintained throughout the study as required by regulations.

10.2 Ethical norms

The study will strictly follow the ethical principles of the Declaration of Helsinki. The IRB/IEC/REB will review all study documents to safeguard the rights, safety and welfare of participants. The study will be conducted only at sites approved by the IRB/IEC/REB. Amendments to the protocol, informed consent form, written information given to participants (including diary cards), and other documents will be submitted by the investigator to the IRB/IEC/REB.

10.3 Informed Consent

Participants should fully understand the contents of the study and sign the informed consent form before participating in this study. The method of obtaining and documenting informed consent and its contents will comply with the requirements of ICH-GCP and all applicable regulations.

10.4 Clinical Monitoring

Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. will conduct inspections and reviews during the study to ensure that the study complies with GCP guidelines. Monitoring activities will be conducted by Shanghai Hezhui Biopharmaceutical Technology Co., Ltd., or designated third party designated monitors, including on-site review of eCRF integrity and clarity, cross-validation with source documents, reconciliation of other matters required by regulatory requirements, etc. The review of medical records will be conducted in a manner that ensures participant privacy.

The monitor will ensure that the investigator complies with the protocol design and regulatory requirements by frequent correspondence (letter, telephone, fax). Regulatory authorities, IRBs/IECs/REBs, and/or sponsors (or designated third parties) have access to all source documents, CRFs, and other study documents at the time of on-site verification. Sponsors need to ensure that these documents are readily accessible to support these activities.

10.5 Protocol Amendment

The investigator will conduct the clinical study in accordance with the protocol provided by Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. The protocol will be approved by the IRB/IEC/REB and the corresponding regulatory authorities. The protocol contents may not be modified without the consent of the sponsor and the investigator. Protocol amendments need to be approved by the IRB/IEC/REB, unless they directly threaten the rights and interests of participants. Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. will ensure compliance with regulatory requirements and submit all protocol amendments to regulatory authorities. Substantial amendments to the protocol can be made only after approval by regulatory authorities and the IRB/IEC/REB. When protocol deviations that pose a direct hazard to participants need to be immediately eliminated, the investigator should contact Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. as circumstances permit to discuss the action plan. All deviations from the protocol need to be fully documented.

10.6 Data Quality Control

To ensure the accuracy, completeness and reliability of the data, Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. or its designated third party will perform the following:

- Provide guidance materials to sites as needed;
- Provide training as needed to guide investigators and clinical coordinators. Specific training content will involve the protocol, CRFs and study procedures;
- Regular visits to the study site;
- Maintain contact with site staff by mail, telephone, and/or fax;
- Review and assess CRF data and/or use standard computer editing to detect errors in data collection;
- Perform a quality review of the database.

In addition, Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. or its representatives will be inspected based on participant data samples recorded in the site source documents. Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. and/or regulatory authorities may review the study at any time.

10.7 Data Collection Tools/Source Data

The CRF Data for this study will be completed using an Electronic Data Capture (EDC) system, and all source records will be defined and retained by the site, and all records of source Data entered into the EDC system will be retained.

10.8 Participant Confidentiality Measures

To maintain participant privacy, all CRFs, investigational product records, study reports,

and correspondence will identify participants by designated participant numbers. The study personnel will grant monitors and inspectors access to the participant ' s original medical records to Shanghai Hezhui Biopharmaceutical Technology Co., Ltd. or its designees and regulatory authorities to verify the data collected on the CRFs and review the data collection process. To the extent permitted by applicable laws and regulations, the privacy of participants will be strictly protected from disclosure.

10.9 **Record Retention**

The investigator will retain all study records as required by ICH-GCP and other applicable regulations. If the investigator is no longer responsible for the retention of study records, regulatory authority needs to be transferred to other persons willing to assume responsibility. Shanghai He Gloria Biopharmaceutical Technology Co., Ltd. shall be notified in writing of any change in custody.

10.10 **Liability and Insurance**

Shanghai Hezhu Biopharmaceutical Technology Co., Ltd. has signed the coverage scope of the insurance strategy in the terms of the study, and the legal liability for injury to the participants will be scientifically verified in strict accordance with applicable laws and professional standards.

10.11 **Publication of Study Results and Use of Information**

All ABSK061-related information provided to the investigator by the sponsor is confidential. The investigator may use this information to complete the study and may not be used for other purposes without the consent of the sponsor. The investigator is obligated to provide the sponsor with complete data obtained during the study. Information obtained during the clinical study will be used for the development of ABSK061 and may be disclosed to regulatory authorities, other investigators, business partners, and consultants as needed.

11 References

12 Appendix

12.1 Strong CYP3A inducers and inhibitors

Listed below are strong inducers or inhibitors of the CYP3A family and concomitant use with ABSK061 should be prohibited, except for non-systemic use.

Strong CYP3A inducers a
Apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
Strong CYP3A inhibitors b
Boceprevir, clarithromycin, cobicistat, danoprevir and ritonavir, etegravir and ritonavir, grapefruit, idelaris, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, palitonavir and ritonavir and (obinasabuvir and/or dasabuvir), posaconazole, ritonazole, ritonavir, saquinavir and ritonavir, telaprevir, telithromycin, telithromycin and ritonavir, troleandomycin, voriconazole

CYP = cytochrome P450

This list does not list all cases in detail. Similar restrictions apply to other drugs known to potently modulate CYP3A activity. Please contact the Sponsor on your own initiative if you have any questions.

(a) fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-andinducers#table3-3 (Accessed 25 August 2020).

(b) fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-andinducers#table3-2 (Accessed 25 August 2020).