Clinical Study Protocol

Human Bioequivalence Study of Letermovir Tablets

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Protocol Summary

Item	Content
Study Title	Human Bioequivalence Study of Letermovir Tablets
Drug Name	Letermovir Tablets
Primary Objective	To study the pharmacokinetics of a single oral dose of the test product letermovir tablets and the reference product letermovir tablets (Prevymis®) in healthy adult subjects under fasting/fed conditions, and to evaluate the bioequivalence of the two oral formulations under fasting/fed conditions.
Secondary Objective	To study the safety of the test product letermovir tablets and the reference product Prevymis® in healthy subjects.
Overall Design	Single-center, open-label, randomized, single-dose, two-period, two-sequence, crossover study design.
Drug Information	Test product T: Letermovir tablets, specification: 0.24 g, batch number: to be provided, manufacturing date: to be provided, expiry date: to be provided, manufactured and

provided by Qilu Pharmaceutical Co., Ltd. Storage: sealed storage below 30°C. The test product used for subjects comes from the same batch.

Reference product R: Letermovir tablets (trade name: Prevymis®), specification: 240 mg, batch number: X015822, expiry date: February 21, 2026, manufactured by MSD International GmbH T/A MSD Ireland (Ballydine) (Ireland), provided by Qilu Pharmaceutical Co., Ltd. Storage: sealed storage below 30°C. The reference product used for subjects comes from the same batch.
Number of Subjects28 healthy subjects planned for each of the fasting and fed studies, with a total of 56 healthy subjects planned.
Washout Period At least 7 days
Study Duration At least 25 days, including a 14-day screening period and at least an 11-day study period.
In-House Stay In each period, subjects will be admitted to the Phase I Clinical Research Center on the day before dosing and remain in the center for at least 72 h after dosing.
Study Design This study is a single-center, open-label, randomized, single-dose, two-period, two-sequence, crossover bioequivalence study in healthy adult subjects.

The fasting and fed studies each plan to enroll 28 healthy subjects, and randomization is performed separately for the fasting and fed studies. According to the randomization table, subjects will be randomly assigned to one of two groups (Group A: T-R; Group B: R-T). The washout period between the two administrations is at least 7 days. All subjects will receive the corresponding drug according to the randomization table on Day 1 of Period 1 and Day 8 of Period 2. The crossover administration scheme is shown below.
Crossover Administration Scheme
Group Sequence Period 1 Period 2
Group A T-R Test product T Reference product R
Group B R-T Reference product R Test product T
Study Procedures
Screening Period
After signing the written informed consent, subjects will undergo screening examinations within 14 days before the first dose. The investigator will check the inclusion and exclusion criteria based on screening examinations and interview results.

First Admission
Subjects who pass preliminary screening will arrive at the Phase I Clinical Research Center on Day -1 (the day before dosing). Admission-related examinations and interviews will be performed. The investigator will determine subject eligibility based on the screening period and Day -1 examination results. Eligible subjects will enter the study and be randomized.

Fasting Study
After fasting for at least 10 h, all subjects are expected to start dosing at approximately 08:00 (±1 h) on Day 1 of each period. According to the randomization table, subjects will take the corresponding drug in the fasting state with 240 mL warm water.

Venous blood samples of approximately 3 mL will be collected at pre-dose 0 h (within 60 min before dosing) and at 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0 and 72.0 h after dosing, for a total of 20 time points. Each blood sample will be collected into a vacuum blood collection tube containing KEDTA anticoagulant and centrifuged. The centrifuged plasma sample will be divided into two portions for pharmacokinetic analysis.

Vital signs (including body temperature, pulse and blood pressure) will be measured at pre-dose 0 h (within 60 min before dosing), and at 2 h (±30 min), 6 h (±30 min), 12 h (±60 min), 24 h (±60 min), 48 h (±60 min) and 72 h (±60 min) after dosing.

After completing blood collection and vital sign examination at 72.0 h after dosing in Period 1, subjects may leave the Phase I Clinical Research Center after approval. Before leaving, staff will inform subjects of precautions during the washout period and instruct them to report any adverse events occurring during the washout period.

Taking a 7-day washout period as an example, after the 7-day washout period, subjects will return to the research center on Day 7 of the trial. At the time of admission for Period 2, admission-related examinations and interviews will be conducted. The investigator will determine whether the subject should withdraw or continue in the study based on the examination results. All procedures in Period 2 are the same as those in Period 1. Subjects will leave the Phase I Clinical Research Center after completing safety examinations on Day 11 of Period 2.

If an AE occurs during the study, follow-up is required until the AE resolves or stabilizes, or the subject is lost to follow-up or refuses follow-up.

Fed Study

After fasting for at least 10 h, subjects will start eating a high-fat high-calorie meal 30 min before dosing and finish the meal within 30 min. At approximately 08:00 (±1 h), the first subject will start dosing 30 min after starting the meal, taking the corresponding drug with 240 mL warm water.

Other procedures are the same as in the fasting study.

Dosing Procedure

Fasting study: After fasting for at least 10 h, subjects will take the test product (T) letermovir tablets or the reference product (R) letermovir tablets Prevymis® with 240 mL warm water. One 240 mg tablet will be taken orally in each period.

Fed study: After fasting for at least 10 h, subjects will start eating a high-fat high-calorie meal 30 min before dosing and finish the meal within 30 min. At 30 min after starting the meal, subjects will take the test product (T) letermovir tablets or the reference product (R) letermovir tablets Prevymis® with 240 mL warm water. One 240 mg tablet will be taken orally in each period.

Route of administration: Oral administration. Subjects should remain seated during the entire

dosing process and be supervised by trained staff. The investigational product must be swallowed whole and must not be chewed, crushed or split. To ensure compliance with the dosing procedure, staff should check the subject's hands and mouth after dosing.

Subject Restrictions

Subjects should avoid strenuous exercise. On the dosing day of each period, subjects should maintain an upright upper body position within 2 h after dosing (except for necessary activities); if a subject needs to go to the bathroom within 4 h after dosing, research staff should accompany them.

In the event of an adverse event or other special circumstances, with the consent of the principal investigator or study physician, the subject's position may be changed. This situation will not be recorded as a protocol deviation.

Dietary and Fluid Restrictions

Both the fasting and fed groups will fast from fluids within 1 h before and after dosing in each period (except for the 240 mL warm water required for dosing and beverages contained in the high-fat high-calorie meal).

Subjects will fast for at least 10 h before fasting administration or before eating the high-fat high-calorie breakfast (fed group). They will fast for 4 h after dosing, and then eat a standard lunch 4 h after dosing. The meal times on the dosing day of each period should be approximately the same. The diet plan for all subjects during the in-house period will be uniformly specified. If meals, vital sign monitoring and blood sample collection conflict, blood sample collection and vital sign monitoring will be prioritized.

Medication Restrictions

During the study, no drugs (including contraceptives) or health products are allowed except for drugs used to treat adverse events. Any drug other than the investigational product used during the study should be recorded in detail in the source documents and case report forms (if concomitant medication is used during hospitalization, it should be recorded to the minute). Once a subject needs to use other drugs outside the protocol during the study (including the washout period), the principal investigator will decide whether the subject should continue in the study based on whether the non-investigational drug interacts with the investigational product and the action and elimination time of the non-investigational drug.

Blood Sample Collection

Each blood sample of approximately 3 mL will be collected into a pre-labeled vacuum blood collection tube containing K2EDTA anticoagulant. If an intravenous indwelling needle is used for PK blood collection, approximately 1 mL of blood should be discarded before each collection, and the indwelling needle should be sealed with normal saline after each collection. After each blood collection, the tube should be gently inverted several times to mix, and immediately placed in crushed ice or an ice-water mixture.

Record the actual blood collection time. The allowable deviation ranges are as follows:

Collection Time Point	Allowable Deviation
0 h	-60 min
0.5 h–4.0 h	±1 min
4.5 h–12.0 h	±3 min
24.0 h–72.0 h	±10 min

Blood collection beyond this deviation range may be defined as a protocol deviation.

Blood Sample Processing

Centrifugation should begin within 1 h after blood collection. Blood samples will be centrifuged at 1700 g at approximately 4°C (2–8°C) for 10 min. The upper plasma will be aspirated and divided into two portions and transferred to labeled cryovials. Approximately 0.6 mL plasma will be placed in the test tube, and the remaining plasma will be placed in the backup tube. The centrifuged plasma samples should be placed in crushed ice or an ice-water mixture and must be placed in a refrigerator within 2 h after blood collection. After plasma separation, samples may be temporarily stored in a -20°C refrigerator, transferred to an ultra-low temperature freezer (below -60°C) within 24 h, or directly stored in an ultra-low temperature freezer (below -60°C) after separation. Store until sample transport. Record abnormal phenomena during processing (such as hemolysis, spillage, etc.). Collection and pretreatment of biological samples should be performed under white light conditions.

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled:

Voluntarily sign the informed consent form before the trial and fully understand the trial content, procedures and possible adverse reactions;

Be able to complete the study according to the protocol requirements;

Subjects are willing to have no pregnancy, sperm donation or egg donation plans from the time of signing informed consent (female subjects have taken effective contraceptive measures within 14 days before the first dose) until 6 months after the last dose, and voluntarily take effective contraceptive measures;

Male and female subjects aged 18 years or older (including 18 years) and without reproductive needs;

Male subjects must weigh at least 50.0 kg, female subjects must weigh at least 45.0 kg, and body mass index (BMI) = weight/height² (kg/m²) must be within the range of 19.0–26.0 kg/m² (including boundary values).

Exclusion Criteria

Subjects with any of the following conditions will be excluded:

Have a serious history of heart, liver, kidney, gastrointestinal, nervous system, endocrine system, respiratory system or psychiatric abnormalities, and the study physician considers it inappropriate to participate;

Have clinically significant abnormalities judged by a clinician, including physical examination, vital sign examination, electrocardiogram or clinical laboratory tests;

Have a specific allergy history (such as asthma) or current allergic diseases (such as urticaria, eczema), or an allergic constitution (such as allergy to two or more drugs, foods such as milk or pollen), or known allergy to the components of this drug or similar drugs;

Have dysphagia or any history of gastrointestinal disease affecting drug absorption (such as gastric or small bowel resection, atrophic gastritis, gastrointestinal bleeding, obstruction, etc.);

Female subjects who are pregnant, breastfeeding, or have a positive pregnancy test result;

Any one or more of hepatitis B surface antigen, hepatitis C antibody, HIV antibody or syphilis antibody is positive;

Have a history of drug abuse within five years, or have used drugs within 3 months before screening, or have a positive urine drug screening;

Have an average weekly alcohol consumption of more than 14 units within 3 months before screening (1 unit = 360 mL beer or 45 mL spirits with 40% alcohol or 150 mL wine), or cannot stop alcohol intake from 24 h before dosing until completion of blood sample collection in that period, or have a positive alcohol breath test;

Have an average daily smoking amount of more than 5 cigarettes within 3 months before screening or refuse not to use tobacco products during the in-house period;

Have a history of surgery within 3 months before screening, or plan to undergo surgery during the study period;

Have donated blood or suffered massive blood loss (>400 mL, excluding physiological blood loss in women) within 3 months before the first dose, or donated platelets ≥2 therapeutic doses within 1 month (1 therapeutic dose = 12 U platelets);

Have participated in any drug clinical trial and taken medication within 3 months before the first dose;

Have used any drug that interacts with letermovir within 30 days before dosing (such as antibiotics: nafcillin; anticonvulsants: carbamazepine, phenobarbital, phenytoin; antimycobacterials: rifabutin, rifampin; antipsychotics: thioridazine; endothelin antagonists:

bosentan; herbal products: St. John's wort; HIV drugs: efavirenz, etravirine, nevirapine; immunosuppressants: cyclosporine; wake-promoting agents: modafinil; ergot alkaloids: ergotamine, dihydroergotamine; HMG-CoA reductase inhibitors: rosuvastatin, pitavastatin, simvastatin; pimozide; dabigatran);

Have received live attenuated vaccine within 7 days before the first dose, or plan to receive live attenuated vaccine during the study;

Have used any prescription drug within 14 days before the first dose;

Have used any over-the-counter drug, Chinese herbal medicine or health product within 7 days before the first dose;

Have consumed special diets (such as glucose and glucose-containing products) or engaged in strenuous exercise within 48 h before the first dose, or have other factors affecting drug absorption, distribution, metabolism or excretion;

Have consumed any food rich in xanthine substances (such as coffee, tea, chocolate, cocoa, milk tea, etc.) within 48 h before the first dose;

Have difficulty with venous blood collection or a history of needle phobia or blood phobia;

Have special dietary requirements and cannot comply with the provided diet and corresponding regulations;

Other subjects deemed unsuitable for participation by the investigator.

Withdrawal Criteria and Management
Investigator-determined withdrawal: After randomization, if a subject develops a condition unsuitable for continuing the trial, the investigator may decide to withdraw the subject.

A. The investigator considers it necessary to stop the trial from a medical ethics perspective;

B. An adverse event (AE) occurs, and the investigator judges that the subject should not continue the trial;

C. The investigator judges that withdrawal is in the best interest of the subject;

D. Poor compliance, and the investigator judges that the subject should not continue, including but not limited to:

a) The subject does not use the drug or undergo examinations as required;

b) The subject uses other drugs or foods that affect safety evaluation and pharmacokinetic results;

c) The subject violates the protocol regarding smoking and alcohol;

d) The subject has other behaviors affecting the trial results.

Subject-initiated withdrawal: The subject withdraws informed consent, or although the subject has not withdrawn informed consent, no longer accepts medication and examinations, or is lost to follow-up (also considered withdrawal or dropout).

Management: Regardless of whether withdrawal is requested by the subject or considered by the principal investigator, if a subject withdraws during the trial, the reason for withdrawal should be recorded. For safety reasons, subjects who withdraw early after taking the investigational product need safety examinations after withdrawal. The investigator must make appropriate efforts to contact subjects lost to follow-up. If the subject cannot be contacted after at least 3 telephone calls, it will be recorded as lost to follow-up.

Exclusion Criteria for Analysis

Before statistical analysis, the principal investigator, sponsor and data statistician will jointly determine whether individual cases should be excluded. Whether to exclude the corresponding data of a subject should be comprehensively judged based on factors such as the degree of trial completion and the reason for withdrawal, and relevant explanations should be provided, including but not limited to the following:

Subjects who do not meet inclusion criteria or meet exclusion criteria and are judged not to be exempt from enrollment;

Subjects who vomit within twice the median Tmax after dosing;

Subjects whose pre-dose blood sample concentration is greater than 5% of Cmax;

Subjects whose first sample is Cmax and for whom early samples (5–15 min) were not collected;

During the trial, subjects have behaviors that violate the trial plan, and reasonable judgment is made according to the severity of the protocol deviation;

Subjects have other behaviors during the trial that may affect pharmacokinetics.

Pharmacokinetic Parameters

Based on the plasma concentration data of letermovir, pharmacokinetic parameters will be estimated by non-compartmental model. The estimated pharmacokinetic parameters include AUC0-t, AUC0-∞, AUC_%Extrap, Cmax, Tmax, t1/2 and λz.

Safety Evaluation Indicators

Safety evaluation indicators will be evaluated through adverse events, serious adverse events,

adverse reactions, vital signs, physical examination, laboratory tests (blood routine, blood biochemistry and urinalysis), 12-lead electrocardiogram and other examinations.

Statistical Methods and Analysis

The letermovir plasma concentration data obtained will be used to calculate pharmacokinetic parameters using WinNonlin V8.2 or SAS V9.4 or above.

Primary PK parameters: Cmax, AUC0-t, AUC0-∞

Secondary PK parameters: Tmax, t1/2, λz, AUC_%Extrap

The primary and secondary PK parameters of letermovir will be calculated. After natural logarithmic transformation of the primary pharmacokinetic parameters AUC0-t, AUC0-∞ and Cmax of letermovir, administration sequence, formulation and administration period will be treated as fixed effects, and subject individual (nested within sequence) will be treated as a random effect for analysis of variance (ANOVA). The geometric mean ratio of the test product to the reference product and its 90% confidence interval will be calculated.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 26.1 or above). The incidence rate will be summarized according to the test product and reference product groups. All adverse events, their severity and relationship to the drug will be described in list form. Changes in vital signs, physical examination, laboratory tests (blood routine, blood biochemistry and urinalysis) and electrocardiogram results before and after the trial will be analyzed.

Bioequivalence Evaluation

The bioequivalence evaluation of the test product and reference product of letermovir tablets is based on the pharmacokinetic parameters AUC0-t, AUC0-∞ and Cmax of letermovir. When the 90% confidence intervals of the geometric mean ratios of AUC0-t, AUC0-∞ and Cmax of letermovir between the test product and the reference product do not exceed the equivalence interval of 80.00–125.00%, the two formulations are considered bioequivalent.

Flowchart

Assessment Procedure	Screening Period	Period 1					Period 2				End of Study or Early Termination
Study Stage	D-14 to D-1	D-1	D1	D2	D3	D4	D5–D6	D7	D8	D9	D10 D11
Informed consent	X										
Demographics	X										
Medical/surgical history	X										
Physical examination	X	X									
Infectious disease screening	X										
Blood biochemistry, blood routine, urinalysis		X	X								
12-lead ECG	X	X									
Vital signs assessment[1]	X	X	X	X	X	X	X	X	X	X	X X

Urine drug screening[2]	X	X	X	X												
Alcohol breath test	X	X														
Pregnancy test[3]	X	X	X	X	X											
Verify/review inclusion and exclusion criteria					X	X										
Randomization	X															
Admission to Phase I Clinical Research Center						X	X	X	X	X	X	X	X			
Discharge from clinical research center										X				X		
High-fat high-calorie standard meal (fed study only)								X						X		
Single-dose administration			X						X							
PK blood sample collection			X	X	X	X	X	X	X	X	X	X				
Concomitant medication and non-drug treatment							X	X	X	X	X	X	X			
Adverse events		X	X	X	X	X	X	X								

Vital signs assessment (blood pressure, pulse and body temperature) will be performed during screening, at admission, at pre-dose 0 h (within 60 min before dosing), and at 2 h (±30 min), 6 h (±30 min), 12 h (±60 min), 24 h (±60 min), 48 h (±60 min), 72 h (±60 min) after dosing, and after early termination.

Urine drug screening will be performed during screening and at admission; if screening is performed on Day -1, urine drug screening at admission on Day -1 may be omitted.

Female subjects will undergo urine pregnancy test during screening, and blood pregnancy test at admission during the study period and at the end of study or early termination; if screening is performed on Day -1, only blood pregnancy test will be performed.

Abbreviations

Abbreviation	Full Name
AE	Adverse Event
AUC	Area Under the Concentration-Time Curve
AUC0-∞	Area Under the Concentration-Time Curve from Time 0 to Infinity
AUC0-t	Area Under the Concentration-Time Curve from Time 0 to the Last Measurable Concentration Collection Time t
AUC_%Extrap	Percentage of Residual Area. Calculated as [(AUC0-∞ - AUC0-t)/AUC0-∞] × 100%
Cmax	Maximum Drug Concentration
CMV	Cytomegalovirus
CRF	Case Report Form
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GVHD	Graft-versus-Host Disease

HBsAg Hepatitis B Virus Surface Antigen
HIV Human Immunodeficiency Virus
HSCT Hematopoietic Stem Cell Transplantation
ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
kg Kilogram
L Liter
mg Milligram
mL Milliliter
NMPA National Medical Products Administration
PET Preemptive Therapy
PK Pharmacokinetics
SAE Serious Adverse Event
SOP Standard Operating Procedure
t1/2 Drug Half-Life
Tmax Time to Peak Concentration

1 Study Background

1.1 Rationale

Cytomegalovirus (CMV) is a double-stranded DNA virus of the herpesvirus genus, mainly transmitted through direct contact. CMV infection is prevalent worldwide. The CMV seropositivity rates among healthy people over 14 years old, blood donors and organ donors worldwide are 83% and 86%, respectively; the seropositivity rate of CMV in healthy adults in China exceeds 90%. CMV disease can cause high post-transplantation mortality. For example, the mortality rate of CMV pneumonia can be as high as 80%–90% or more. It also increases the risk of bacterial and fungal opportunistic infections, and increases the risk of graft-versus-host disease (GVHD) and non-relapse mortality. Clinically, timely and appropriate prevention and treatment of CMV infection is very important. Specific methods include: 1) antiviral drug prophylaxis, but currently there is no drug approved in China for the prevention of CMV infection after hematopoietic stem cell transplantation (HSCT); 2) preemptive therapy (PET), which involves active monitoring of viral replication and use of anti-CMV drugs when CMV viremia is detected.

Currently, commonly approved anti-CMV drugs worldwide (whether for prophylaxis or PET) are nucleoside analogues with toxicity (including myelosuppression and nephrotoxicity), which limits their clinical application. Ganciclovir and valganciclovir, the most widely used drugs for treating CMV infection and disease, are associated with myelosuppression. The second-line drug foscarnet is usually associated with nephrotoxicity. Cidofovir is usually used as a third-line drug, and its use is associated with myelosuppression and renal impairment. Currently approved anti-CMV drugs in China mainly include ganciclovir, valganciclovir and foscarnet, but none are approved for the prevention and treatment of CMV infection in HSCT.

Letermovir tablets (trade name: Prevymis) is an antiviral drug developed by Merck. It was first approved by the FDA in 2017, then by the EMA in 2018, and was approved for import in China in 2021 for the prevention of CMV infection and CMV disease in CMV-seropositive adult recipients after allogeneic HSCT.

To meet clinical needs, Qilu Pharmaceutical Co., Ltd. has developed letermovir tablets, which belongs to Category 4 chemicals according to chemical drug registration classification requirements. The purpose of this study is to compare the differences in absorption rate and extent between letermovir tablets from Qilu Pharmaceutical Co., Ltd. and letermovir tablets manufactured by MSD International GmbH T/A MSD Ireland (Ballydine) (Ireland), and to evaluate whether the two are bioequivalent.

1.2 Basic Information of the Study Drug
Generic name: Letermovir Tablets
Molecular formula: $C_{29}H_{28}F_4N_4O_4$
Molecular weight: 572.55
Chemical name: (4S)-2-{8-fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5-(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl}acetic acid

1.3 Clinical Application of the Study Drug
1.3.1 Mechanism of Action
Letermovir inhibits the CMV DNA terminase complex pUL51, pUL56 and pUL89 (a terminase complex required for viral replication). Biochemical characterization and electron microscopy show that letermovir affects the formation of properly unit-length genomes and interferes with virion maturation. Resistance virus genotype characterization confirms that the target of letermovir is the CMV DNA terminase complex.

1.3.2 Indication
This product is used for the prevention of CMV infection and CMV disease in CMV-seropositive adult recipients [R+] receiving allogeneic hematopoietic stem cell transplantation (HSCT).

1.3.3 Dosage and Administration
General information: Take with or without food. Swallow whole; do not split, crush or chew.

Letermovir injection contains hydroxypropyl betadex and is only suitable for patients who cannot receive oral therapy. Once patients can take oral medication, they should switch to oral letermovir immediately. The tablet and injection forms of this product can be used interchangeably according to the physician’s judgment, and no dose adjustment is required when switching dosage forms.

Missed dose: Patients should be instructed that if a dose is missed, it should be taken as soon as possible when remembered. If the patient remembers the missed dose at the time of the next dose, they should be instructed to skip the missed dose and take the next dose according to the regular schedule. Patients should be instructed not to double the dose at the next dose or take more than the prescribed dose.

Recommended adult dose: The recommended dose of this product is 480 mg once daily.

This product should be started after HSCT. It can be started on the day of transplantation or no later than 28 days after transplantation. This product can be started before or after engraftment. It should be continued until 100 days after transplantation.

Adult dose adjustment: If this product is used concomitantly with cyclosporine, the dose of this product should be reduced to 240 mg once daily.

If cyclosporine is started after initiation of this product, the next dose of this product should be reduced to 240 mg once daily.

If cyclosporine is stopped after initiation of this product, the next dose of this product should be increased to 480 mg once daily.

If cyclosporine administration is temporarily interrupted due to high cyclosporine blood concentration, no adjustment of this product dose is required.

CMV DNA monitoring: The safety and efficacy of letermovir for prophylaxis have been established in patients with negative CMV DNA test results. Monitor CMV DNA once weekly until Week 14 after transplantation, then once every two weeks until Week 24. In the case of clinically significant CMV DNAemia or disease, discontinue letermovir prophylaxis and initiate standard preemptive therapy (PET) or treatment. For patients who have received letermovir prophylaxis and subsequently have a positive baseline CMV DNA test result, if PET criteria are not met, prophylaxis may be continued.

Special populations:

Pediatric patients: The safety and efficacy of this product in pediatric patients under 18 years of age are not clear.

Elderly patients: No dose adjustment is required based on age.

Patients with renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment. There are no data in patients with end-stage renal disease (CrCl <10 mL/min), regardless of whether they receive dialysis.

Patients with hepatic impairment: No dose adjustment is required for patients with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment. This product is not recommended for patients with severe (Child-Pugh C) hepatic impairment.

This product is not recommended for patients with moderate hepatic impairment combined with moderate or severe renal impairment.

1.3.4 Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates

observed in the clinical trials of one drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Allogeneic HSCT adult recipients who are CMV-seropositive [R+]
The safety of this product was evaluated in a randomized, double-blind, placebo-controlled Phase III study (P001). A total of 565 subjects were randomized to the letermovir group (N=373) or placebo group (N=192) and received 14 weeks of treatment after transplantation. An adverse event refers to an adverse event reported by a subject during treatment with the study drug or within two weeks after completion/discontinuation of study drug treatment. Because more patients in the placebo group discontinued treatment early, the average reporting period for adverse events and laboratory abnormalities in the letermovir group was approximately 22% longer than that in the placebo group.

In the letermovir group, the most common adverse reactions occurring in at least 1% of subjects and at a higher frequency than the placebo group were: nausea (7.2%), diarrhea (2.4%) and vomiting (1.9%).

The most common adverse reactions leading to discontinuation of this product were nausea (1.6%), vomiting (0.8%) and abdominal pain (0.5%).

Overall, the proportion of subjects who discontinued due to adverse events was similar between groups (letermovir group 13% vs placebo group 12%). One subject experienced hypersensitivity with moderate dyspnea after switching from oral administration to the first intravenous dose, leading to treatment discontinuation.

Cardiac adverse events
Compared with subjects receiving placebo, subjects receiving this product had a higher incidence of cardiac adverse events (regardless of investigator-assessed causality) (letermovir group 13% vs placebo group 6%). The most common cardiac adverse events were tachycardia (letermovir group 4% vs placebo group 2%) and atrial fibrillation (letermovir group 3% vs placebo group 1%). Among subjects with one or more cardiac adverse events, 85% in the letermovir group and 92% in the placebo group reported events of mild or moderate severity.

Summary table of adverse reactions
Adverse reactions in patients using this product in clinical trials are listed below. The table lists adverse reactions by system organ class and frequency. Frequency definitions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), or very rare (<1/10,000).

Table 1: Adverse Reactions of Letermovir

Frequency	Adverse Reaction
Immune system disorders	Uncommon: Hypersensitivity
Metabolism and nutrition disorders	Uncommon: Decreased appetite

Nervous system disorders Uncommon: Dysgeusia, headache
Ear and labyrinth disorders Uncommon: Vertigo
Gastrointestinal disorders Common: Nausea, diarrhea, vomiting; Uncommon: Abdominal pain
Hepatobiliary disorders Uncommon: Alanine aminotransferase increased, aspartate aminotransferase increased
Musculoskeletal and connective tissue disorders Uncommon: Muscle spasms
Renal and urinary disorders Uncommon: Blood creatinine increased
General disorders and administration site conditions Uncommon: Fatigue, peripheral edema
Laboratory abnormalities
Overall, the proportion of subjects with potentially clinically significant laboratory values (blood routine and biochemistry, including renal and hepatic function) was similar between the letermovir and placebo groups.

Selected laboratory abnormalities with potential clinical significance occurring during treatment or within 2 weeks after stopping treatment are shown in the table below.

Table 2: Selected Laboratory Abnormalities with Potential Clinical Significance in Study P001

Laboratory Parameter Letermovir Group N=373 Placebo Group N=192
Absolute neutrophil count (cells/μL) <500 19% 19%
500–<750 4% 7%
750–<1000 8% 9%
Hemoglobin (g/dL) <6.5 2% 1%
6.5–<8.0 14% 15%
8.0–<9.5 41% 43%
Platelets (cells/μL) <25000 27% 21%
25000–<50000 17% 18%
50000–<100000 20% 30%
Serum creatinine (mg/dL) >2.5 2% 3%
>1.5–2.5 17% 20%
The median time to engraftment (defined as absolute neutrophil count ≥500/mm³ for 3 consecutive days after transplantation) was 19 days and 18 days in the letermovir and placebo groups, respectively.

1.3.5 Precautions and Contraindications
Contraindications
This product is contraindicated in patients who are allergic to letermovir or any inactive ingredient in this product.

Pimozide
When this product is used concomitantly with pimozide, because letermovir inhibits cytochrome P450 (CYP3A), pimozide blood concentration may increase, leading to QT interval prolongation and torsades de pointes.

Ergot alkaloids
When this product is used concomitantly with ergot alkaloids (ergotamine and dihydroergotamine), because letermovir inhibits CYP3A, ergot alkaloid concentrations may increase, leading to ergotism.

Cyclosporine with rosuvastatin, pitavastatin or simvastatin
When this product is used concomitantly with cyclosporine, rosuvastatin, pitavastatin or simvastatin blood concentrations may increase significantly, leading to myopathy or rhabdomyolysis. In the prescribing information for these statins, concomitant use with cyclosporine is contraindicated. Consistent with the prescribing information for these statins, when letermovir is used concomitantly with cyclosporine, concomitant use of these statins is contraindicated.

Cyclosporine with dabigatran
Concomitant use of dabigatran with cyclosporine may increase dabigatran plasma concentration, which may be accompanied by an increased risk of bleeding. In the dabigatran prescribing information, concomitant use with cyclosporine is contraindicated. Consistent with the dabigatran prescribing information, when letermovir is used concomitantly with cyclosporine, concomitant use of dabigatran is contraindicated.

Precautions
Risk of adverse reactions or decreased therapeutic effect due to drug interactions
Concomitant use of this product with certain drugs may cause known or potential significant drug interactions, some of which may lead to the following risks:

Increased exposure to concomitant drugs or this product, which may lead to clinically significant adverse reactions.

Significantly decreased plasma concentration of concomitant drugs, leading to decreased therapeutic effect of concomitant drugs.

For steps to prevent or manage these known or potential significant drug interactions, including dosing recommendations, see Table 4.

Caution should be exercised when this product is used concomitantly with CYP3A substrate drugs with a narrow therapeutic window (such as alfentanil, fentanyl and quinidine), because such concomitant use may increase plasma concentrations of CYP3A substrate drugs. Close monitoring and/or dose adjustment of concomitant CYP3A substrate drugs is recommended.

Use in pregnant and breastfeeding women
Pregnancy: There are no adequate human data to determine whether this product poses a risk to pregnancy outcomes. In rats and rabbits, embryotoxicity was observed at maternal toxicity systemic AUC exposures approximately 11 times and 2 times the AUC at the recommended human dose (RHD), respectively. In a rat prenatal and postnatal development study, no

developmental toxicity was observed up to the highest maternal systemic AUC exposure (approximately 2 times the AUC at RHD). To calculate the safety margin, the AUC at RHD is defined as the mean AUC in HSCT recipients receiving 480 mg intravenous administration.

For the applicable population of this product, the background risk of major birth defects and miscarriage is unknown. The potential risk of this product to humans is unknown. This product should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus.

Breastfeeding: It is not known whether letermovir is secreted in human milk, affects human milk secretion, or affects the breastfed child. When administered to lactating rats, letermovir was detected in milk and in the blood of breastfed pups. The benefits of breastfeeding for infant development and health, the mother's clinical need for this product, and any potential adverse effects of this product or the mother's underlying disease on the breastfed infant should be considered.

Females and males of reproductive potential
Infertility: There are no data on the effect of letermovir on human fertility. Decreased fertility due to testicular toxicity was observed in male rats.

Pediatric use: The safety and efficacy of this product in patients under 18 years of age are not clear.

Geriatric use: In a Phase III clinical trial in HSCT recipients, safety and efficacy results were similar between elderly and younger subjects.

Patients with renal impairment: For patients with CLcr greater than 10 mL/min (according to the Cockcroft-Gault equation), no dose adjustment of letermovir is required based on renal impairment. The safety of letermovir in patients with end-stage renal disease (CLcr less than 10 mL/min), including dialysis patients, is unknown.

Patients with hepatic impairment: No dose adjustment of letermovir is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Letermovir is not recommended for patients with severe (Child-Pugh C) hepatic impairment.

1.3.6 Drug Interactions
Pharmacodynamic interactions
Effects of other drugs on letermovir
Letermovir is a substrate of organic anion transporting polypeptide 1B1/3 (OATP1B1/3) and P-glycoprotein (P-gp) transporters and UDP-glucuronosyltransferase 1A1/3 (UGT1A1/3) enzymes. Concomitant use of this product with OATP1B1/3 transporter inhibitors may increase letermovir plasma concentration. When this product is used concomitantly with cyclosporine (a potent inhibitor of P-gp and OATP1B1/3), the recommended dose of this product is 240 mg once daily.

Concomitant use of this product with strong and moderate inducers of transporters (such as P-gp) and/or enzymes (such as UGT) is not recommended because such concomitant use may decrease letermovir plasma concentration.

When rifampin is used concomitantly with this product, letermovir plasma concentration initially increases (due to rifampin inhibition of OATP1B1/3), which is not clinically significant. If rifampin is continued, letermovir plasma concentration decreases in a clinically significant manner.

Effects of letermovir on other drugs
Concomitant use of this product with midazolam increases midazolam plasma concentration, suggesting that letermovir is a moderate inhibitor of CYP3A. When this product is used concomitantly with CYP3A substrate drugs, plasma concentrations of concomitant CYP3A substrate drugs may increase in a clinically significant manner.

Letermovir is an inhibitor of OATP1B1/3 transporters. Concomitant use of this product with OATP1B1/3 transporter substrate drugs may increase plasma concentrations of concomitant OATP1B1/3 substrates in a clinically significant manner.

Known and other potential drug interactions
If the dose of a concomitant drug is adjusted due to concomitant use with this product, the dose should be readjusted after completion of treatment with this product.

When this product is used concomitantly with cyclosporine, the combined effect on CYP3A substrates may be similar to that of a strong CYP3A inhibitor. Please refer to the prescribing information for CYP3A substrate drugs regarding dosing information when used concomitantly with strong CYP3A inhibitors.

When this product is used concomitantly with cyclosporine, the combined effect on CYP3A and OATP1B1/3 substrate drugs may differ from the effect of this product alone. Please refer to the prescribing information for the concomitant drug and cyclosporine.

Table 3 lists known or potential clinically significant drug interactions. The described drug interactions are based on studies conducted with this product or expected potential drug interactions with this product.

Table 3: Potentially Significant Drug Interactions: Recommendations Based on Drug Interaction Study Results or Expected Interactions

Concomitant Drug Class and/or Clearance Pathway: Drug Name Effect on Blood Concentration Clinical Comments and Recommendations
Antiarrhythmic: amiodarone Amiodarone ↑ When this product is used concomitantly with amiodarone, amiodarone plasma concentration increases. During concomitant use, close monitoring for amiodarone-related adverse events is recommended. Amiodarone blood

concentration should be monitored frequently.

Antibiotic: nafcillin Letermovir ↓ When this product is used concomitantly with nafcillin, this product plasma concentration may decrease. Concomitant use of this product with nafcillin is not recommended.

Anticoagulant: warfarin Warfarin ↓ When this product is used concomitantly with warfarin, warfarin plasma concentration may decrease. When warfarin is used concomitantly with this product, INR should be monitored frequently.

Anticonvulsant: carbamazepine Letermovir ↓ When this product is used concomitantly with carbamazepine, this product plasma concentration may decrease. Concomitant use of this product with carbamazepine is not recommended.

Anticonvulsant: phenobarbital Letermovir ↓ When this product is used concomitantly with phenobarbital, this product plasma concentration may decrease. Concomitant use of this product with phenobarbital is not recommended.

Anticonvulsant: phenytoin Letermovir ↓; phenytoin ↓ When this product is used concomitantly with phenytoin, this product plasma concentration may decrease. This product may decrease phenytoin plasma concentration. Concomitant use of this product with phenytoin is not recommended.

Antidiabetic: glyburide Glyburide ↑ When this product is used concomitantly with glyburide, glyburide plasma concentration may increase.

Antifungal: voriconazole* Voriconazole ↓ When this product is used concomitantly with voriconazole, voriconazole plasma concentration decreases. If concomitant use of this product and voriconazole is necessary, close monitoring for decreased voriconazole efficacy is recommended.

Antimycobacterial: rifabutin Letermovir ↓ When this product is used concomitantly with rifabutin, this product plasma concentration may decrease. Concomitant use of this product with rifabutin is not recommended.

Antimycobacterial: rifampin* Letermovir ↓ When this product is used concomitantly with rifampin, this product plasma concentration decreases. Concomitant use of this product with rifampin is not recommended.

Antipsychotic: thioridazine Letermovir ↓ When this product is used concomitantly with thioridazine, this product plasma concentration may decrease. Concomitant use of this product with thioridazine is not recommended.

Endothelin antagonist: bosentan Letermovir ↓ When this product is used concomitantly with bosentan, this product plasma concentration may decrease. Concomitant use of this product with bosentan is not recommended.

Herbal product: St. John’s wort (Hypericum perforatum) Letermovir ↓ When this product is used concomitantly with St. John’s wort, this product plasma concentration may decrease. Concomitant use of this product with St. John’s wort is not recommended.

HIV drug: efavirenz Letermovir ↓ When this product is used concomitantly with efavirenz, this product plasma concentration may decrease. Concomitant use of this product with efavirenz is not recommended.

HIV drug: etravirine Letermovir ↓ When this product is used concomitantly with etravirine, this product plasma concentration may decrease. Concomitant use of this product with etravirine is not recommended.

HIV drug: nevirapine Letermovir ↓ When this product is used concomitantly with nevirapine,

this product plasma concentration may decrease. Concomitant use of this product with nevirapine is not recommended.

HMG-CoA reductase inhibitor: atorvastatin* Atorvastatin ↑ When this product is used concomitantly with atorvastatin, atorvastatin plasma concentration increases. Close monitoring for statin-related adverse events, such as myopathy, is recommended. When atorvastatin is used concomitantly with this product, the atorvastatin dose should not exceed 20 mg/day.

HMG-CoA reductase inhibitors: pitavastatin, rosuvastatin, simvastatin Pitavastatin ↑, rosuvastatin ↑, simvastatin ↑ Concomitant use of this product with pitavastatin, rosuvastatin or simvastatin is not recommended. When this product is used concomitantly with cyclosporine, pitavastatin, rosuvastatin or simvastatin are contraindicated.

Other HMG-CoA reductase inhibitors: fluvastatin, lovastatin, pravastatin HMG-CoA reductase inhibitor concentration ↑ This product may increase statin plasma concentration. Close monitoring for statin-related adverse events, such as myopathy, is recommended. Dose adjustment of these drugs may be needed when used concomitantly with this product.

Immunosuppressant: cyclosporine++ Cyclosporine ↑; letermovir ↑ When this product is used concomitantly with cyclosporine, blood concentrations of both this product and cyclosporine increase. When this product is used concomitantly with cyclosporine (a potent inhibitor of OATP1B1/3), the dose of this product should be reduced to 240 mg once daily. Cyclosporine whole blood concentration should be monitored frequently during and after treatment with this product, and the cyclosporine dose should be adjusted accordingly.

Immunosuppressant: sirolimus++ Sirolimus ↑ When this product is used concomitantly with sirolimus, sirolimus blood concentration increases. Sirolimus whole blood concentration should be monitored frequently during and after treatment with this product, and the sirolimus dose should be adjusted accordingly.

Immunosuppressant: tacrolimus++ Tacrolimus ↑ When this product is used concomitantly with tacrolimus, tacrolimus plasma concentration increases. Tacrolimus whole blood concentration should be monitored frequently during and after treatment with this product, and the tacrolimus dose should be adjusted accordingly.

Proton pump inhibitors: omeprazole, pantoprazole Omeprazole ↓, pantoprazole ↓ When this product is used concomitantly with these proton pump inhibitors (PPIs), PPI plasma concentration may decrease. When PPIs are used concomitantly with this product, clinical monitoring and dose adjustment may be needed.

Wake-promoting agent: modafinil Letermovir ↓ When this product is used concomitantly with modafinil, this product plasma concentration may decrease. Concomitant use of this product with modafinil is not recommended.

CYP2C8 substrates*: repaglinide, rosiglitazone CYP2C8 substrate concentration ↑ This product may increase plasma concentration of CYP2C8 substrates. During concomitant use of this product with repaglinide or rosiglitazone, frequent monitoring of blood glucose concentration is recommended.

CYP3A substrates: alfentanil, fentanyl, midazolam, quinidine CYP3A substrate concentration ↑ This product may increase plasma concentration of CYP3A substrates. When this product is used concomitantly with CYP3A substrate drugs, please refer to the prescribing information for CYP3A substrate drugs regarding dosing information when used concomitantly with moderate CYP3A inhibitors. During concomitant use, frequent monitoring for adverse reactions related to

these drugs is recommended. Dose adjustment of CYP3A substrate drugs may be needed.
This table does not include all drug interactions.

↓ = decrease; ↑ = increase
± These interactions have been studied.
§ Please refer to the corresponding prescribing information.

Based on physiologically based pharmacokinetic modeling.
Drugs that do not have clinically significant interactions with this product
When this product is used concomitantly with itraconazole (a P-gp/BCRP inhibitor), no clinically significant interaction occurs.

In clinical studies, after concomitant use with this product, plasma concentrations of digoxin (a P-gp substrate) and acyclovir (an OAT3 substrate) did not show clinically significant changes.

Drug interactions of letermovir with the following drugs have been evaluated in clinical studies: mycophenolate mofetil, fluconazole, posaconazole and oral contraceptives. No dose adjustment is required when this product is used concomitantly with these drugs.

Pharmacokinetic interactions
Effect of cyclosporine
In HSCT recipients, concomitant use of letermovir with cyclosporine increases letermovir plasma concentration. When used concomitantly with cyclosporine, the bioavailability of this product after 240 mg once daily oral administration is estimated to be approximately 85%. When used concomitantly with cyclosporine, the recommended dose of this product is 240 mg once daily.

Drug interaction studies of this product with potentially concomitant drugs or with drugs commonly used as pharmacokinetic interaction probes were conducted in healthy subjects (see Tables 4 and 5).

In vitro studies show that letermovir is a substrate of OATP1B1/3, P-gp, UGT1A1 and UGT1A3. OATP1B1/3 transporter inhibitors may increase letermovir plasma concentration. When this product is used concomitantly with cyclosporine (a potent inhibitor of OATP1B1/3), the recommended dose of this product is 240 mg once daily. Changes in letermovir plasma concentration caused by itraconazole inhibition of P-gp/BCRP are not clinically significant. Inhibition of UGT is expected to have no clinically significant effect on letermovir plasma concentration. Induction of drug enzymes (such as UGT) and/or transporters (such as P-gp) by rifampin may cause a clinically significant decrease in letermovir plasma concentration; therefore, concomitant use of strong and moderate inducers with this product is not recommended. Although CYP3A, CYP2D6 and CYP2J2 have been found to mediate letermovir metabolism in vitro, oxidative metabolism is considered a minor elimination pathway based on human in vivo data.

In vitro, letermovir is a time-dependent inhibitor and inducer of CYP3A. Concomitant use of this product with midazolam increases midazolam exposure, indicating that the net effect of letermovir

on CYP3A is moderate inhibition (see Table 4). Based on these results, concomitant use of this product with CYP3A substrates may increase plasma concentrations of CYP3A substrates. In vitro, letermovir is a reversible inhibitor of CYP2C8. Using physiologically based pharmacokinetic model predictions, plasma concentrations of CYP2C8 substrates will increase when used concomitantly with this product. When used concomitantly with this product, voriconazole exposure decreases, most likely due to induction of voriconazole elimination pathways (CYP2C9 and CYP2C19) by this product. Concomitant use of this product with CYP2C9 and CYP2C19 substrate drugs will lead to decreased plasma concentrations of CYP2C9 and CYP2C19 substrate drugs. In vitro, letermovir is an inducer of CYP2B6; its clinical significance is unclear.

In vitro, letermovir inhibits efflux transporters P-gp, breast cancer resistance protein (BCRP), bile salt export pump (BSEP), multidrug resistance-associated protein 2 (MRP2), OAT3 and hepatic uptake transporters OATP1B1/3. Concomitant use of this product with OATP1B1/3 transporter substrate drugs (such as atorvastatin, which is a known CYP3A substrate, OATP1B1/3 substrate and possible BCRP substrate) may cause a clinically significant increase in plasma concentrations of OATP1B1/3 substrate drugs. In clinical studies, after concomitant use with this product, plasma concentrations of digoxin (a P-gp substrate) or acyclovir (an OAT3 substrate) did not show clinically significant changes (see Table 5). The effects of letermovir on BCRP, BSEP and MRP2 substrates have not been evaluated in clinical studies; their clinical significance is unclear.

Table 4: Drug Interactions: Changes in Letermovir Pharmacokinetics When Used Concomitantly

Concomitant Drug Concomitant Drug Regimen Letermovir Regimen N Geometric Mean Ratio of Letermovir PK With/Without Concomitant Drug [90% CI] (No Effect = 1.00): AUC, Cmax, C24hr*

Antifungal: fluconazole 400 mg single oral dose 480 mg single oral dose 14 AUC 1.11 (1.01, 1.23); Cmax 1.06 (0.93, 1.21); C24hr 1.28 (1.15, 1.43)

Antifungal: itraconazole 200 mg once daily oral 480 mg once daily oral 14 AUC 1.33 (1.17, 1.51); Cmax 1.21 (1.05, 1.39); C24hr 1.90 (1.58, 2.28)

Antimycobacterial: rifampin 600 mg single oral 480 mg single oral 16 AUC 2.03 (1.84, 2.26); Cmax 1.59 (1.46, 1.74); C24hr 2.01 (1.59, 2.54)

Antimycobacterial: rifampin 600 mg single IV 480 mg single oral 16 AUC 1.58 (1.38, 1.81); Cmax 1.37 (1.16, 1.61); C24hr 0.78 (0.65, 0.93)

Antimycobacterial: rifampin 600 mg once daily oral 480 mg once daily oral 14 AUC 0.81 (0.67, 0.98); Cmax 1.01 (0.79, 1.28); C24hr 0.14 (0.11, 0.19)

Antimycobacterial: rifampin 600 mg once daily oral (24 h after rifampin dose)* 480 mg once daily oral 14 AUC 0.15 (0.13, 0.17); Cmax 0.27 (0.22, 0.31); C24hr 0.09 (0.06, 0.12)

Immunosuppressant: cyclosporine 200 mg single oral 240 mg once daily oral 12 AUC 2.11 (1.97, 2.26); Cmax 1.48 (1.33, 1.65); C24hr 2.06 (1.81, 2.35)

Immunosuppressant: mycophenolate mofetil 1 g single oral 480 mg once daily oral 14 AUC 1.18 (1.04, 1.32); Cmax 1.11 (0.92, 1.34); C24hr 1.39 (1.12, 1.74)

Immunosuppressant: tacrolimus 5 mg single oral 80 mg twice daily oral 14 AUC 1.02 (0.97, 1.07); Cmax 0.92 (0.84, 1.00); C24hr 1.02 (0.93, 1.12)

Tacrolimus is C12hr value.

† These data are for letermovir administration 24 h after the last rifampin dose, reflecting the effect of rifampin on letermovir.

Table 5: Drug Interactions: Pharmacokinetics of Concomitant Drugs When Letermovir Is Present or Used Concomitantly

Concomitant Drug	Concomitant Drug Regimen	Letermovir Regimen	N	Geometric Mean Ratio of Concomitant Drug PK With/Without Letermovir [90% CI] (No Effect = 1.00): AUC, Cmax
CYP3A substrate: midazolam	1 mg single IV	240 mg once daily oral	16	AUC 1.47 (1.37, 1.58); Cmax 1.05 (0.94, 1.17)
CYP3A substrate: midazolam	2 mg single oral	240 mg once daily oral	16	AUC 2.25 (2.04, 2.48); Cmax 1.72 (1.55, 1.92)
P-gp substrate: digoxin	0.5 mg single oral	240 mg twice daily oral	22	AUC 0.88 (0.80, 0.96); Cmax 0.75 (0.63, 0.89)
Immunosuppressant: cyclosporine	50 mg single oral	240 mg once daily oral	14	AUC 1.66 (1.51, 1.82); Cmax 1.08 (0.97, 1.19)
Immunosuppressant: mycophenolate mofetil	1 g single oral	480 mg once daily oral	14	AUC 1.08 (0.97, 1.20); Cmax 0.96 (0.82, 1.12)
Immunosuppressant: tacrolimus	5 mg single oral	480 mg once daily oral	13	AUC 2.42 (2.04, 2.88); Cmax 1.57 (1.32, 1.86)
Immunosuppressant: sirolimus	2 mg single oral	480 mg once daily oral	13	AUC 3.40 (3.01, 3.85); Cmax 2.76 (2.48, 3.06)
Antifungal and antiviral: acyclovir	400 mg single oral	480 mg once daily oral	13	AUC 1.02 (0.87, 1.2); Cmax 0.82 (0.71, 0.93)
Antifungal: fluconazole	400 mg single oral	480 mg single oral	14	AUC 1.03 (0.99, 1.08); Cmax 0.95 (0.92, 0.99)
Antifungal: itraconazole	200 mg once daily oral	480 mg once daily oral	14	AUC 0.76 (0.71, 0.81); Cmax 0.84 (0.76, 0.92)
Antifungal: posaconazole	300 mg single oral	480 mg once daily oral	13	AUC 0.98 (0.82, 1.17); Cmax 1.11 (0.95, 1.29)
Antifungal: voriconazole	200 mg twice daily oral	480 mg once daily oral	12	AUC 0.56 (0.51, 0.62); Cmax 0.61 (0.53, 0.71)
HMG-CoA reductase inhibitor: atorvastatin	20 mg single oral	480 mg once daily oral	14	AUC 3.29 (2.84, 3.82); Cmax 2.17 (1.76, 2.67)
Oral contraceptive: ethinyl estradiol (EE)/levonorgestrel (LNG)	0.03 mg EE single oral; 0.15 mg LNG single oral	480 mg once daily oral	22	EE: AUC 1.42 (1.32, 1.52); Cmax 0.89 (0.83, 0.96); LNG: AUC 1.36 (1.30, 1.43); Cmax 0.95 (0.86, 1.04)

1.4 Basis for Selection of Reference Product

Letermovir was developed by Merck & Co. in the United States and was approved by the U.S. FDA in 2017 for the prevention of CMV infection and CMV disease in CMV-seropositive adult recipients [R+] receiving allogeneic hematopoietic stem cell transplantation (HSCT). According to the NMPA “Catalogue of Reference Preparations for Generic Drugs (Sixty-Sixth Batch)” (Serial No. 66-20), letermovir tablets (Prevymis, 240 mg, marketed in China) held by Merck Sharp &

Dohme B.V. were selected as the reference product.

1.5 Declaration Specification

The specification of letermovir tablets produced by Qilu Pharmaceutical Co., Ltd. is 0.24 g. The bioequivalence study results of letermovir tablets 0.24 g in this study will be used to declare the 0.24 g specification of letermovir tablets.

2 Study Objectives

Primary Objective

To study the pharmacokinetics of a single oral dose of the test product letermovir tablets and the reference product letermovir tablets (Prevymis) in healthy adult subjects under fasting/fed conditions, and to evaluate the bioequivalence of the two oral formulations under fasting/fed conditions.

Secondary Objective

To study the safety of the test product letermovir tablets and the reference product Prevymis in healthy subjects.

3 Basis for Study Design

This protocol is mainly formulated in accordance with or with reference to the Declaration of Helsinki (promulgated June 1964, latest revision October 2013); the Drug Administration Law of the People's Republic of China (promulgated September 20, 1984, latest revision August 26, 2019); the Drug Registration Administration Measures (promulgated December 1, 2002, latest revision January 22, 2020); the Good Clinical Practice (promulgated March 2, 1998, latest revision April 26, 2020, effective July 1, 2020); the Chinese Pharmacopoeia 2020 Edition Appendix 9011 Guidelines for Human Bioavailability and Bioequivalence Studies of Pharmaceutical Preparations (released July 3, 2020); the Guidelines for Management of Phase I Clinical Trials of Drugs (Trial) (released December 2, 2011); the Guidelines for Management of Drug Clinical Trial Biosample Analysis Laboratories (Trial) (released December 2, 2011); the Technical Guidelines for Human Bioequivalence Studies of Generic Chemical Drugs Using Pharmacokinetic Parameters as Endpoint Evaluation Indicators (released March 2016); and other relevant regulations and reported adverse reactions.

3.2 Pharmacokinetic Characteristics

General introduction

The pharmacokinetics of letermovir were studied after oral and intravenous administration in healthy subjects and HSCT recipients.

In healthy subjects, after single and multiple oral or intravenous administration of letermovir 240 mg and 480 mg, letermovir exposure increased in a greater than dose-proportional manner. Letermovir is rapidly absorbed, with a median time to peak plasma concentration (Tmax) of 1.5–3.0 h, and declines in a biphasic manner. After 480 mg once daily oral administration of this product, the geometric mean steady-state AUC and Cmax values were 71,500 ng·hr/mL and 13,000 ng/mL, respectively. The post-absorption plasma concentration-time curve after oral

administration of letermovir is similar to that observed after intravenous administration. Letermovir clearance (CL) reaches steady state in 9 to 10 days, with an AUC accumulation ratio of 1.22 and a Cmax accumulation ratio of 1.03.

In HSCT recipients, population pharmacokinetic analysis using Phase III trial data estimated letermovir AUC (see Table 6). Differences in exposure among treatment regimens are not clinically significant; efficacy was consistent across the exposure range observed in P001.

Table 6: Letermovir AUC (ng·hr/mL) in HSCT Recipients

Treatment Regimen	Median (90% Prediction Interval)*
480 mg oral, without cyclosporine	34,400 (16,900, 73,700)
480 mg IV, without cyclosporine	100,000 (65,300, 148,000)
240 mg oral, with cyclosporine	60,800 (28,700, 122,000)
240 mg IV, with cyclosporine	70,300 (46,200, 106,000)

Median and 90% prediction interval are based on simulations using a Phase III population PK model with inter-individual variability.

Absorption

In healthy subjects, based on population pharmacokinetic analysis, the estimated absolute bioavailability of letermovir is approximately 94% over the dose range of 240 mg to 480 mg. In HSCT recipients, after 480 mg once daily oral administration of this product (without cyclosporine), the estimated bioavailability of letermovir is approximately 35%. The inter-individual variability of bioavailability is estimated to be approximately 37%.

Distribution

According to population pharmacokinetic analysis, the estimated mean steady-state volume of distribution of letermovir after intravenous administration in HSCT recipients is 45.5 L.

In vitro, letermovir is extensively bound to human plasma proteins (98.7%). The blood-to-plasma distribution ratio of letermovir is 0.56, independent of the concentration range evaluated in vitro (0.1–10 mg/L).

In preclinical distribution studies, letermovir was distributed in organs and tissues, with the highest concentrations observed in the gastrointestinal tract, bile duct and liver, and low concentrations observed in the brain.

Metabolism

Most drug-related components in plasma are the parent drug (96.6%). No major metabolites were detected in plasma. Letermovir is partially eliminated through UGT1A1/1A3-mediated glucuronidation.

Excretion

According to population pharmacokinetic analysis, the estimated steady-state CL of letermovir

after intravenous administration in HSCT recipients is 4.84 L/hr. The inter-individual variability of CL is estimated to be approximately 24.6%.

After oral administration of radiolabeled letermovir, 93.3% of radioactivity was recovered in feces. Most of the drug was excreted as the parent drug, with a small amount (6% of the dose) excreted in feces as an acyl-glucuronide metabolite. Urinary excretion of letermovir is negligible (<2% of the dose).

3.3 Previous Bioequivalence Studies

Effect of food on the PK of letermovir

In a randomized, open-label, single-dose, two-period, two-treatment, two-sequence, crossover study, the effect of a high-fat meal on the PK of letermovir was evaluated. The study enrolled 14 healthy female subjects aged 18–55 years (including boundary values). According to the protocol, subjects received 480 mg letermovir orally after a high-fat meal (Group A) and in the fasting state (Group B), respectively. Plasma samples were collected for PK analysis up to 72 h after dosing. The results showed that the ratios of Cmax and AUC (fed/fasted) were 1.30 (1.04, 1.62) and 1.00 (0.84, 1.17), respectively. One outlier subject (No. 9) had Cmax and AUC ratios of ~6 and ~3, respectively. After excluding this subject from PK analysis, the effect on exposure ratios was minimal [Cmax and AUC ratios were 1.22 (1.15, 1.30) and 0.95 (0.90, 1.01), respectively]. The median Tmax under fed and fasting conditions was 2.5 h and 2.76 h, respectively. PK parameters are shown in Table 7.

Table 7: PK Parameters of Oral Letermovir Under Fasting and Fed Conditions

(The original OCR table is garbled and could not be reliably reconstructed. Please refer to the source protocol for the complete table.)

4 Study Design

4.1 Overall Design

This study uses a single-center, open-label, randomized, single-dose, two-period, two-sequence, crossover, fasting and fed administration study design.

4.2 Study Population

With reference to the NMPA bioequivalence guidelines, this study will enroll healthy adult male and female subjects aged 18 years or older (including boundary values).

4.3 Sample Size Determination

According to the Technical Guidelines for Human Bioequivalence Studies of Generic Chemical Drugs Using Pharmacokinetic Parameters as Endpoint Evaluation Indicators, “the number of enrolled subjects should meet the requirement that the bioequivalence evaluation has sufficient statistical power” for sample size estimation.

Currently, exact information on the intra-individual variability of letermovir tablets has not been collected. Based on data from the original manufacturer’s food effect study, the intra-individual variability of letermovir is estimated to be 17%. Assuming 17%, a geometric mean ratio of the test

product to the reference product of 0.95, power of 0.90, and two one-sided significance level of 0.05, 20 subjects are needed to achieve equivalence. Due to subject dropout and other uncertain factors, this study plans to enroll 28 healthy subjects each for the fasting and fed bioequivalence studies, with a total of 56 healthy subjects planned.

4.4 Blinding

This clinical study is an open-label study. Except for the pharmacokinetic analysis testing personnel, other personnel such as clinical investigators, project management personnel, project monitors, data management and statistical analysis personnel are not blinded. The analysis testing personnel will use blinded analysis and will not know which formulation the subject received in each period during sample analysis.

4.5 Randomization

4.5.1 Randomization Method

Randomization is performed separately for the fasting and fed studies in this study. A block randomization method is used. A randomization table will be generated using SAS V9.4 or above software, and subjects will be randomly divided into two groups (Group A (T-R), Group B (R-T)) at a 1:1 ratio. The order in which each subject will receive the test product and reference product will be determined according to the randomization table. The randomization seed will be retained so that the randomization can be reproduced. The subject randomization table will be directly transmitted to the clinical site by the randomization statistician before the start of the trial.

4.5.2 Randomization Allocation Principles

At screening, the informed consent form is signed (represented as SXXX).

Screening identification: Screening numbers are assigned according to the order in which subjects sign the informed consent form to identify subjects. The subject screening number consists of “S” plus three characters—“SXXX”, where S represents screening and XXX is the sequence number, such as “S001”.

Enrollment randomization: After subjects pass screening and admission examinations, they will be randomized to obtain a unique randomization number. Randomization is performed separately for the fasting and fed studies. Subjects who pass screening will be assigned a “randomization number” in the order of screening numbers. For the fasting study group, the “randomization number” is represented by “1XXX”; for the fed study group, the “randomization number” is represented by “2XXX”. For example, “1003” indicates the 3rd subject entering the fasting study, and “2005” indicates the 5th subject entering the fed study.

For subjects who have been randomized, regardless of the reason for withdrawal, their randomization number will be retained, and the subject will not be allowed to re-enter the trial.

4.6 Washout Period

The elimination half-life of letermovir is approximately 12 h. The washout period should be greater than 7 half-lives. Considering the feasibility of the trial, the washout period in this study is

set to at least 7 days.

4.7 Study Duration
The screening period before subject dosing is 14 days.

The entire trial process from Day 1 of Period 1 to the end of Period 2 requires at least 11 days.

4.8 Sample Collection Design
According to the Technical Guidelines for Human Bioequivalence Studies of Generic Chemical Drugs Using Pharmacokinetic Parameters as Endpoint Evaluation Indicators, there should be sufficient sampling points at each phase of the plasma concentration-time curve and around the expected peak time, including absorption, distribution and elimination phases. Literature data show that the Tmax of letermovir is approximately 1.5–3 h, and the mean plasma half-life is approximately 12 h.

With reference to the human pharmacokinetic characteristics of letermovir reported in domestic and international studies, the following blood collection time points are designed: pre-dose 0 h (within 60 min before dosing) and 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0 and 72.0 h after dosing, collecting approximately 3 mL of venous blood each time.

4.9 High-Fat High-Calorie Meal
According to NMPA guidelines, subjects will eat a high-fat (providing approximately 50% of food calories) high-calorie (approximately 800–1000 kcal) breakfast after fasting for at least 10 h. Subjects will start eating 30 min before dosing and finish the meal before dosing. Protein provides approximately 150 kcal, carbohydrates provide approximately 250 kcal, and fat provides approximately 500–600 kcal. The high-fat high-calorie meal recipes in the two periods should be the same.

5 Investigational Product
5.1 Investigational Product Information
Test product T: Letermovir tablets, specification: 0.24 g, batch number: to be provided, manufacturing date: to be provided, expiry date: to be provided, manufactured and provided by Qilu Pharmaceutical Co., Ltd. Storage: sealed storage below 30°C. Administration method: oral. The test product used for subjects comes from the same batch.

Reference product R: Letermovir tablets (trade name: Prevymis), specification: 240 mg, batch number: X015822, manufacturing date: February 22, 2023, expiry date: February 21, 2026, held by Merck Sharp & Dohme B.V., manufactured by MSD International GmbH T/A MSD Ireland (Ballydine) (Ireland), provided by Qilu Pharmaceutical Co., Ltd. Storage: sealed storage below 30°C. Administration method: oral. The reference product used for subjects comes from the same batch.

In addition to the above information, the packaging of the investigational product should also

include the drug number, clinical trial project number, and the label “Caution: For Clinical Trial Use Only” or similar wording.

5.2 Receipt, Dispensing and Storage of Investigational Product

The transport of investigational product should be accompanied by at least an inspection report, a transport list and a receipt confirmation form for research institution personnel.

The pharmacist or designated personnel at the research center are responsible for receiving, storing, dispensing and returning the drug, and completing corresponding records.

When the clinical trial ward receives the investigational product, it must sign the drug receipt, verify and accept on the spot, and sign and date it, in duplicate, with the clinical study site and sponsor each keeping one copy. The investigational product should be stored according to the storage conditions required for the test product and reference product. Drug management follows GCP requirements, and the research institution must designate dedicated personnel, dedicated cabinets, and locked storage. Drug management personnel or investigators will dispense the investigational product according to the subject’s “randomization number” and randomization table. The use of each investigational product, packaging recovery after administration, recovery of remaining or unused drugs, etc., should be recorded in a dedicated record form in a timely manner, reviewed and signed by two persons.

The investigational product is stored according to the storage conditions in 5.1. The test product and reference product used for all subjects must each come from the same batch.

5.3 Administration Method

On Day 1 and Day 8 of the trial, subjects will take the test product letermovir tablets or the reference product Prevymis according to the randomization table.

Fasting administration regimen: After fasting for at least 10 h, subjects will take the test product (T) letermovir tablets or the reference product (R) letermovir tablets Prevymis with 240 mL warm water. One 240 mg tablet will be taken orally in each period.

Fed administration regimen: After fasting for at least 10 h, subjects will start eating a high-fat high-calorie meal 30 min before dosing and finish the meal within 30 min. At 30 min after starting the meal, subjects will take the test product (T) letermovir tablets or the reference product (R) letermovir tablets Prevymis with 240 mL warm water. One 240 mg tablet will be taken orally in each period.

Dosing procedure: Oral administration. Subjects should remain seated during the entire dosing process and be supervised by trained staff. The investigational drug must be swallowed whole and must not be chewed, crushed or split. To ensure subject compliance with the dosing procedure, staff should check the subject’s hands and mouth after dosing.

Drinking water is prohibited within 1 h before and after dosing (except for the 240 mL warm

water required for dosing and beverages contained in the high-fat high-calorie standard meal). Subjects should maintain an upright upper body position within 2 h after dosing (except for necessary activities). Food is prohibited within 4 h after dosing, and a uniform lunch will be eaten 4 h after dosing. Strenuous exercise should be avoided during the trial.

5.4 Retention Samples of Investigational Product

The test product should be randomly sampled by the sponsor from a production line manufactured under GMP conditions and be qualified by testing. The sponsor will provide qualified and sufficient investigational product (test product and reference product) to the clinical research institution, indicating the batch number, and provide a drug inspection report. The quantity should meet the requirements of the trial and relevant regulations. Before the sponsor provides the investigational product to the clinical research institution, retention samples must not be separated from the investigational product, to ensure that the retention samples are from the same batch of product provided by the sponsor to the clinical research institution for clinical trials. The clinical research institution will extract clinical trial drugs and retention drugs from all investigational product samples provided by the sponsor according to the drug randomization table. If there is any remaining drug extracted for trial administration after the trial is completed, it will be stored together with the retention drug.

The research institution should properly keep all investigational product and retention samples. Retention samples may be entrusted to an independent third party with suitable conditions for storage, but must not be returned to the sponsor or a third party with interests related to the sponsor. The research institution should be responsible for storing retention samples according to the drug storage conditions and continue to store them for at least 2 years after the drug is marketed according to the storage condition requirements.

6 Subject Screening and Withdrawal

6.1 Informed Consent and Communication Before Study

Subjects must voluntarily sign the informed consent form for this study before participating, to protect the legitimate rights and interests of subjects. The investigator is responsible for fully and comprehensively introducing the purpose of the study, the effects of the drug, possible toxic and side effects, and possible risks to the subjects. Subjects should be informed of their rights, the risks and benefits they will bear, etc.

6.2 Inclusion Criteria, Screening Indicators and Pre-Study Education

This study is divided into fasting and fed studies, with 28 subjects enrolled in each, for a total of 56 healthy subjects.

After signing the written informed consent, subjects will undergo a series of examinations, including: demographic data recording, height and weight measurement, medical history/surgical history/medication history/allergy history/blood donation history/clinical trial history/smoking and alcohol history/drug abuse history interview, physical examination, vital sign assessment (blood pressure, pulse and body temperature), 12-lead electrocardiogram, laboratory tests (blood routine, urinalysis, blood biochemistry, infectious disease screening), female urine pregnancy test and

urine drug screening, etc.

Subjects who pass preliminary screening will return to the hospital on Day -1 of the trial and undergo pre-admission examinations. Only subjects who meet all inclusion criteria and do not meet any exclusion criteria can be enrolled in this study. Before enrollment, the investigator should inform subjects of the trial schedule, requirements during the trial, and management regulations of the research center.

6.2.1 Inclusion Criteria
Subjects must meet all of the following inclusion criteria to be enrolled in this study:

Voluntarily sign the informed consent form before the trial and fully understand the trial content, procedures and possible adverse reactions;

Be able to complete the study according to the protocol requirements;

Subjects are willing to have no pregnancy, sperm donation or egg donation plans from the time of signing informed consent (female subjects have taken effective contraceptive measures within 14 days before the first dose) until 6 months after the last dose, and voluntarily take effective contraceptive measures;

Male and female subjects aged 18 years or older (including 18 years) and without reproductive needs;

Male subjects must weigh at least 50.0 kg, female subjects must weigh at least 45.0 kg, and body mass index (BMI) = weight/height² (kg/m²) must be within the range of 19.0–26.0 kg/m² (including boundary values).

6.2.2 Exclusion Criteria
Subjects with any of the following conditions will be excluded:

Have a serious history of heart, liver, kidney, gastrointestinal, nervous system, endocrine system, respiratory system or psychiatric abnormalities, and the study physician considers it inappropriate to participate;

Have clinically significant abnormalities judged by a clinician, including physical examination, vital sign examination, electrocardiogram or clinical laboratory tests;

Have a specific allergy history (such as asthma) or current allergic diseases (such as urticaria, eczema), or an allergic constitution (such as allergy to two or more drugs, foods such as milk or pollen), or known allergy to the components of this drug or similar drugs;

Have dysphagia or any history of gastrointestinal disease affecting drug absorption (such as gastric or small bowel resection, atrophic gastritis, gastrointestinal bleeding, obstruction, etc.);

Female subjects who are pregnant, breastfeeding, or have a positive pregnancy test result;

Any one or more of hepatitis B surface antigen, hepatitis C antibody, HIV antibody or syphilis antibody is positive;

Have a history of drug abuse within five years, or have used drugs within 3 months before screening, or have a positive urine drug screening;

Have an average weekly alcohol consumption of more than 14 units within 3 months before screening (1 unit = 360 mL beer or 45 mL spirits with 40% alcohol or 150 mL wine), or cannot stop alcohol intake from 24 h before dosing until completion of blood sample collection in that period, or have a positive alcohol breath test;

Have an average daily smoking amount of more than 5 cigarettes within 3 months before screening or refuse not to use tobacco products during the in-house period;

Have a history of surgery within 3 months before screening, or plan to undergo surgery during the study period;

Have donated blood or suffered massive blood loss (>400 mL, excluding physiological blood loss in women) within 3 months before the first dose, or donated platelets ≥2 therapeutic doses within 1 month (1 therapeutic dose = 12 U platelets);

Have participated in any drug clinical trial and taken medication within 3 months before the first dose;

Have used any drug that interacts with letermovir within 30 days before dosing (such as antibiotics: nafcillin; anticonvulsants: carbamazepine, phenobarbital, phenytoin; antimycobacterials: rifabutin, rifampin; antipsychotics: thioridazine; endothelin antagonists: bosentan; herbal products: St. John's wort; HIV drugs: efavirenz, etravirine, nevirapine; immunosuppressants: cyclosporine; wake-promoting agents: modafinil; ergot alkaloids: ergotamine, dihydroergotamine; HMG-CoA reductase inhibitors: rosuvastatin, pitavastatin, simvastatin; pimozide; dabigatran);

Have received live attenuated vaccine within 7 days before the first dose, or plan to receive live attenuated vaccine during the study;

Have used any prescription drug within 14 days before the first dose;

Have used any over-the-counter drug, Chinese herbal medicine or health product within 7 days before the first dose;

Have consumed special diets (such as glucose and glucose-containing products) or engaged in

strenuous exercise within 48 h before the first dose, or have other factors affecting drug absorption, distribution, metabolism or excretion;

Have consumed any food rich in xanthine substances (such as coffee, tea, chocolate, cocoa, milk tea, etc.) within 48 h before the first dose;

Have difficulty with venous blood collection or a history of needle phobia or blood phobia;

Have special dietary requirements and cannot comply with the provided diet and corresponding regulations;

Other subjects deemed unsuitable for participation by the investigator.

6.3 Withdrawal Criteria and Management

Investigator-determined withdrawal: After randomization, if a subject develops a condition unsuitable for continuing the trial, the investigator may decide to withdraw the subject.

A. The investigator considers it necessary to stop the trial from a medical ethics perspective;

B. An adverse event (AE) occurs, and the investigator judges that the subject should not continue the trial;

C. The investigator judges that withdrawal is in the best interest of the subject;

D. Poor compliance, and the investigator judges that the subject should not continue, including but not limited to:

a) The subject does not use the drug or undergo examinations as required;

b) The subject uses other drugs or foods that affect safety evaluation and pharmacokinetic results;

c) The subject violates the protocol regarding smoking and alcohol;

d) The subject has other behaviors affecting the trial results.

Subject-initiated withdrawal: The subject withdraws informed consent, or although the subject has not withdrawn informed consent, no longer accepts medication and examinations, or is lost to follow-up (also considered withdrawal or dropout).

Management: Regardless of whether withdrawal is requested by the subject or considered by the principal investigator, if a subject withdraws during the trial, the reason for withdrawal should be recorded. For safety reasons, subjects who withdraw early after taking the investigational product need safety examinations after withdrawal. The investigator must make appropriate efforts to contact subjects lost to follow-up. If the subject cannot be contacted after at least 3 telephone calls,

it will be recorded as lost to follow-up.

6.4 Exclusion Criteria for Analysis

Before statistical analysis, the principal investigator, sponsor and data statistician will jointly determine whether individual cases should be excluded. Whether to exclude the corresponding data of a subject should be comprehensively judged based on factors such as the degree of trial completion and the reason for withdrawal, and relevant explanations should be provided, including but not limited to the following:

Subjects who do not meet inclusion criteria or meet exclusion criteria and are judged not to be exempt from enrollment;

Subjects who vomit within twice the median Tmax after dosing;

Subjects whose pre-dose blood sample concentration is greater than 5% of Cmax;

Subjects whose first sample is Cmax and for whom early samples (5–15 min) were not collected;

During the trial, subjects have behaviors that violate the trial plan, and reasonable judgment is made according to the severity of the protocol deviation;

Subjects have other behaviors during the trial that may affect pharmacokinetics.

7 Detailed Study Procedures

7.1 Study Flow

This study uses a single-center, open-label, randomized, single-dose, two-period, two-sequence, crossover, fasting and fed administration study design.

This study plans to enroll 28 healthy subjects each for the fasting and fed studies, and randomization is performed separately for the fasting and fed studies. According to the randomization table, subjects will be randomly assigned to one of two groups (Group A: T-R; Group B: R-T). The washout period between the two administrations is at least 7 days. All subjects will receive the corresponding drug according to the randomization table on Day 1 of Period 1 and Day 8 of Period 2. The crossover administration scheme is shown below:

Group	Sequence	Period 1	Period 2
Group A	T-R	Test product T	Reference product R
Group B	R-T	Reference product R	Test product T

Screening:

Before participating in screening, subjects must voluntarily sign the informed consent form. Subjects will then undergo a series of examinations including: demographic data recording, medical history/surgical history/medication history/allergy history/blood donation history/clinical trial history/smoking and alcohol history/drug abuse history interview, height and weight measurement, vital sign assessment (blood pressure, pulse and body temperature), physical

examination, 12-lead electrocardiogram, laboratory tests (blood routine, urinalysis, blood biochemistry, infectious disease screening), female urine pregnancy test and urine drug screening, etc.

Subjects who pass preliminary screening will return to the hospital on Day -1 of the trial and undergo pre-admission interview and examinations, including vital signs, urine drug screening, alcohol breath test, blood pregnancy test (female only). The investigator will verify inclusion and exclusion criteria based on the results of the screening period and Day -1. Only subjects who meet all inclusion criteria and do not meet any exclusion criteria can be enrolled in this study. Eligible subjects will enter the study and be randomized.

Observation period:
Enrolled subjects will be admitted on the day before dosing and start fasting from food but not water before approximately 21:00.

Fasting study
After fasting for at least 10 h, all subjects are expected to start dosing at approximately 08:00 (±1 h) on Day 1 of each period. According to the randomization table, subjects will take the corresponding drug in the fasting state with 240 mL warm water. The drug must be swallowed whole and must not be chewed, crushed or split. During dosing, staff should check the subject's hands and mouth to ensure compliance with the dosing procedure. Subjects should remain seated during the entire dosing process and be supervised by trained staff. Subjects should maintain an upright upper body position within 2 h after dosing (except for necessary activities).

Subjects are prohibited from drinking water within 1 h before and after dosing, and from eating within 4 h after dosing. A standard meal should be eaten 4 h after dosing in each period.

Venous blood samples will be collected at pre-dose 0 h (within 60 min before dosing) and at 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0 and 72.0 h after dosing, for a total of 20 time points. Each blood sample of approximately 3 mL will be collected into a vacuum blood collection tube containing K2EDTA anticoagulant and centrifuged. The centrifuged plasma sample will be divided into two portions for pharmacokinetic analysis.

Vital signs (including body temperature, pulse and blood pressure) will be measured at pre-dose 0 h (within 60 min before dosing), and at 2 h (±30 min), 6 h (±30 min), 12 h (±60 min), 24 h (±60 min), 48 h (±60 min) and 72 h (±60 min) after dosing. Subjects are required to voluntarily report symptoms to the study physician during the trial, and the study physician will confirm and record them. Adverse events will be inquired and recorded using non-leading questions during the trial.

After completing blood collection and vital sign examination at 72.0 h after dosing in Period 1, subjects may leave the Phase I Clinical Research Center after approval. Before leaving the Phase I Clinical Research Center, staff will inform subjects of precautions during the washout period and instruct them to report any adverse events occurring during the washout period.

Taking a 7-day washout period as an example, after the 7-day washout period, subjects will return to the clinical center on Day 7 of the trial. At the time of admission for Period 2, vital signs, urine drug screening, alcohol breath test, blood pregnancy test (female only) and admission interview will be conducted. The investigator will determine whether the subject should withdraw or continue in the study based on the examination results. All procedures in Period 2 are the same as those in Period 1. Subjects will leave the Phase I Clinical Research Center after completing safety examinations on Day 11 of Period 2.

If an AE occurs during the study, follow-up is required until the AE resolves or stabilizes, or the subject is lost to follow-up or refuses follow-up.

Fed study

After fasting for at least 10 h, subjects will start eating a high-fat high-calorie meal 30 min before dosing and finish the meal within 30 min. At approximately 08:00 (±1 h), the first subject will start dosing 30 min after starting the meal, taking the corresponding drug with 240 mL warm water. The drug must be swallowed whole and must not be chewed, crushed or split. During dosing, staff should check the subject's hands and mouth to ensure compliance with the dosing procedure.

Other procedures are the same as in the fasting study.

7.2 Subject Management

7.2.1 Diet and Water

Drinking water is prohibited within 1 h before and after dosing each week (except for the 240 mL warm water required for dosing and beverages contained in the high-fat high-calorie standard meal). Water is allowed freely at other times.

All subjects need to fast for at least 10 h before fasting administration or before eating the high-fat high-calorie standard meal. Subjects will fast for 4 h after dosing in each period, and then eat a standard lunch 4 h after dosing. The meal times on the dosing day of each period should be approximately the same. The diet plan for all subjects during the in-house period will be uniformly specified. If meals, vital sign monitoring and blood sample collection conflict, blood sample collection and vital sign monitoring will be prioritized.

7.2.2 Position

Subjects should avoid strenuous exercise. On the dosing day of each period, subjects should maintain an upright upper body position within 2 h after dosing (except for necessary activities). If a subject needs to go to the bathroom within 4 h after dosing, the investigator should accompany them.

In the event of an adverse event or other special circumstances, with the consent of the principal investigator or study physician, the subject's position may be changed. This situation will not be recorded as a protocol deviation.

Subjects must avoid strenuous physical activity throughout the study.

7.2.3 Concomitant Medication and Treatment

During the study, no drugs (including contraceptives and Chinese herbal medicines) or health products are allowed except for drugs used to treat adverse events. Any drug other than the investigational product used during the study should be recorded in detail in the source documents and case report forms (if concomitant medication is used during hospitalization, it should be recorded to the minute). Once a subject needs to use other drugs outside the protocol during the study (including the washout period), the principal investigator will decide whether the subject should continue in the study based on whether the non-investigational drug interacts with the investigational product and the action and elimination time of the non-investigational drug.

7.2.4 Other Requirements

From the date of signing informed consent and throughout the trial, subjects cannot take any prescription drugs, over-the-counter drugs, Chinese herbal medicines or health products.

From the date of signing informed consent and throughout the trial, subjects should not smoke more than 5 cigarettes per day, and cannot use any tobacco products during the in-house period.

From 48 h before dosing in each period until completion of blood sample collection in that period, subjects cannot consume glucose or glucose-containing products, or any food or drink rich in xanthine substances (such as coffee, tea, chocolate, cocoa, milk tea, etc.).

From 24 h before dosing in each period until completion of blood sample collection in that period, subjects cannot consume any alcohol-containing products.

During hospitalization, subjects cannot consume any food or beverages other than those provided by the research center.

Except for necessary circumstances, subjects should maintain an upright upper body position within 2 h after dosing.

From 48 h before the first dose to the end of the trial, subjects cannot engage in strenuous exercise.

Within two days after the end of blood collection in each period, subjects should avoid operating dangerous machinery (including driving) as much as possible.

During the study, all subjects cannot leave the clinical research center before being allowed.

8 Biological Sample Handling, Transport, Storage and Testing

The purpose of this study is to evaluate the bioequivalence of the test product letermovir tablets and the reference product letermovir tablets (Prevymis) in healthy adult subjects under fasting and fed conditions. According to the FDA bioequivalence guidelines, subject blood will be collected and plasma will be used for analysis.

8.1 Naming Principles of Biological Samples

Before blood sample collection, the blood collection tubes and two plasma sample cryovials will be uniformly numbered and affixed with special waterproof labels. The label must include the following information: protocol number, subject number, period information, collection time point, sample type (test sample or backup sample indication), etc. The cryovial label must not indicate the administered formulation.

8.2 Collection and Pretreatment of Biological Samples

In this study, upper limb venous blood will be collected before and after dosing, and plasma will be separated after pretreatment for plasma drug concentration testing. Venous blood will be collected at pre-dose 0 h (within 60 min before dosing) and at 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0 and 72.0 h after dosing, for a total of 20 time points.

Each blood sample of approximately 3 mL will be collected into a pre-cooled, pre-labeled vacuum blood collection tube containing K2EDTA anticoagulant. If an intravenous indwelling needle is used for PK blood collection, approximately 1 mL of blood should be discarded before each collection, and the indwelling needle should be sealed with normal saline after each collection. After each blood collection, the tube should be gently inverted several times to mix, and immediately placed in crushed ice or an ice-water mixture.

Record the actual blood collection time; the blood collection time should be recorded to the minute. The allowable deviation ranges are as follows:

Collection Time Point	Allowable Deviation
0 h	-60 min
0.5 h–4.0 h	±1 min
4.5 h–12.0 h	±3 min
24.0 h–72.0 h	±10 min

Blood collection beyond this error range may be defined as a protocol deviation.

Centrifugation should begin within 1 h after blood collection. Blood samples will be centrifuged at 1700 g at approximately 4°C (2–8°C) for 10 min. The upper plasma will be aspirated and divided into two portions and transferred to labeled cryovials. Approximately 0.6 mL plasma will be placed in the test tube, and the remaining plasma will be placed in the backup tube. The centrifuged plasma samples should be placed in crushed ice or an ice-water mixture and must be placed in a refrigerator within 2 h after blood collection. After plasma separation, samples may be temporarily stored in a -20°C refrigerator, transferred to an ultra-low temperature freezer (below -60°C) within 24 h, or directly stored in an ultra-low temperature freezer (below -60°C) after separation. Store until sample transport. Record abnormal phenomena during processing (such as hemolysis, spillage, etc.). Collection and pretreatment of biological samples should be performed under white light conditions.

8.3 Transport and Storage of Biological Samples

The sample transfer and receipt process shall be checked by dedicated personnel for sample quantity, storage conditions and sample type. Test samples will be transported to the analytical testing unit. The sample transport process will be undertaken by a professional cold-chain biological sample transport company. Dry ice will be used during sample transport, with temperature monitoring and recording, and detailed sample handover forms. After receiving the samples, the sample testing unit will store them in an ultra-low temperature freezer (below -60°C) with temperature monitoring. Backup samples are generally stored at the sample collection unit. If the backup test samples need to be activated, the testing unit must obtain the sponsor's consent and may transfer them from the sample collection unit only after the testing unit has received the test samples. The transport process is the same as that for test samples. After sample testing is completed, both test samples and backup samples need to be stored in an ultra-low temperature freezer (below -60°C) in accordance with regulations or the sponsor's requirements.

8.4 Drug Concentration Testing

The biological sample analysis of this trial will be performed by Shanghai Xihua Testing Technology Service Co., Ltd., and LC-MS/MS is planned to be used to determine letermovir in plasma. The testing content includes the establishment of the biological sample analysis method, method validation, and analysis and testing of biological samples. Detailed information is provided in the method validation plan and sample analysis plan.

9 Pharmacokinetic Parameters and Safety Evaluation Indicators

9.1 Pharmacokinetic Parameters for Evaluation

According to the actual blood sample collection time points, Phoenix WinNonlin (version 8.2 or above) or SAS V9.4 or above will be used to calculate pharmacokinetic parameters. The pharmacokinetic parameters to be evaluated include:

Parameter Definition

Cmax Maximum plasma drug concentration

AUC0-t Area under the drug concentration-time curve from time 0 to the last sample collection time t at which the concentration can be accurately measured

AUC0-∞ Area under the plasma drug concentration-time curve from time 0 to infinity, AUC0-∞ = AUC0-t + Ct/λz

AUC_%Extrap Percentage of residual area. Calculated as [(AUC0-∞ - AUC0-t)/AUC0-∞] × 100%

λz Terminal phase elimination rate constant. The negative value of the slope obtained by linear regression of the logarithm of plasma concentration against time

Tmax Time to peak drug concentration

t1/2 Elimination half-life, t1/2 = ln(2)/λz

9.2 Safety Evaluation Indicators

Safety evaluation will be conducted through adverse events, serious adverse events, adverse reactions, vital signs, physical examination, laboratory tests (blood routine, blood biochemistry and urinalysis), 12-lead electrocardiogram and other examinations.

9.2.1 Laboratory Test Assessment

Laboratory tests for drug safety assessment in this study include: blood routine, blood biochemistry and urinalysis.

Subjects will undergo blood routine, blood biochemistry and urinalysis at screening, at the end of the study or after early termination safety examination.

Abnormal laboratory test results judged by the investigator as clinically significant after dosing must be recorded as adverse events.

9.2.2 Vital Sign Measurement

Vital signs (blood pressure, pulse, body temperature) will be measured during screening, at admission in each period, at pre-dose 0 h (within 60 min before dosing), and at 2 h (±30 min), 6 h (±30 min), 12 h (±60 min), 24 h (±60 min), 48 h (±60 min) and 72 h (±60 min) after dosing, and at the safety examination after early termination.

Vital sign results judged by the investigator as clinically significant after dosing must be recorded as adverse events.

9.2.3 Electrocardiogram Examination

12-lead electrocardiogram examination will be performed during screening, at the end of the study or after early termination safety examination. During screening, subjects with any clinically significant ECG abnormalities cannot be enrolled. During the entire trial, for subject safety, the investigator may decide to perform additional ECG examinations at any time if necessary. ECG results judged by the investigator as clinically significant after dosing must be recorded as adverse events.

9.2.4 Physical Examination

Physical examination will be performed during screening, at the end of the study or after early termination, including general appearance examination, skin system, head, neck, lymph nodes, chest, abdomen, nervous system and musculoskeletal system examination. Physical examination results judged by the investigator as clinically significant after dosing must be recorded as adverse events.

9.3 Assessment of Adverse Events and Serious Adverse Events

9.3.1 Definition of Adverse Events

Adverse event: Any adverse medical event occurring after a subject receives the investigational product, which may manifest as symptoms and signs, disease or laboratory abnormalities, but is not necessarily causally related to the investigational product.

Events that meet the definition of adverse events include:

(1) Signs, symptoms or clinical sequelae suspected to be caused by drug interactions;
(2) Signs, symptoms or clinical sequelae suspected to be caused by overdose of investigational

product or concomitant medication (overdose itself is not reported as an adverse event/serious adverse event).

9.3.2 Adverse Event Reporting

During the trial, subjects are advised to report any adverse events, and trained staff will ask subjects about any adverse events using non-leading questions. Necessary management of adverse events will be performed by the investigator or physician.

All adverse events (clinical symptoms, signs or diseases) occurring during the trial (including the washout period) should be recorded in the source documents. All adverse events reported by subjects themselves or discovered by staff will be listed separately. The signs and symptoms, severity, date and time of onset (24-hour clock), date and time of resolution (24-hour clock), duration, measures taken, outcome and follow-up of adverse events also need to be recorded.

9.3.3 Criteria for Determining Severity of Adverse Events

CTCAE 5.0 will be used as the standard for grading and determining the severity of adverse events. If CTCAE 5.0 does not contain a specific description of the severity grading of an examination indicator, the following table may be used for determination.

Grade Definition

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

Grade 2: Moderate Requires minor, local or non-invasive treatment; limitation in age-appropriate instrumental activities of daily living (such as preparing meals, shopping, using the telephone, etc.).

Grade 3: Severe or medically significant but not immediately life-threatening Hospitalization or prolongation of hospitalization indicated; disabling; limitation in self-care activities of daily living.

Grade 4: Life-threatening Urgent intervention indicated.

Grade 5: Death related to AE

Note: The semicolon (;) in the grade descriptions means “or”.

*Instrumental activities of daily living limitation refers to: preparing meals, buying groceries or clothes, using the telephone, managing money, etc. **Self-care activities of daily living limitation refers to: bathing, dressing and undressing, feeding, toileting, taking medications, and not being bedridden.

9.3.4 Criteria for Determining Relationship Between Adverse Events and Investigational Drug

According to the criteria for determining the causal relationship between drugs and adverse events, the correlation between adverse events and the investigational product is divided into five levels: definitely related, probably related, possibly related, possibly unrelated, and definitely unrelated. Definitely related, probably related and possibly related are all classified as adverse drug reactions. The total number of adverse drug reaction cases is used as the numerator, and all enrolled cases available for adverse reaction evaluation are used as the denominator to calculate the incidence of

adverse reactions. The five-level classification criteria are as follows:

(1) Temporal relationship: whether there is a reasonable temporal relationship between the drug use and the occurrence of the adverse event;
(2) Known: whether the adverse event conforms to the known adverse event type of the drug;
(3) Dechallenge: whether the adverse event disappears or improves after discontinuation or dose reduction;
(4) Rechallenge: whether the same adverse event reappears after re-use of the suspected drug;
(5) Other explanations: whether the adverse event can be explained by the effects of concomitant drugs, progression of the patient's condition, or other treatments.

Judgment Result	Judgment Indicators: 1 Temporal Relationship	2 Known	3 Dechallenge	4 Rechallenge	5 Other Explanations
Definitely related	+	+	+	+	-
Probably related	+	+	+	?	-
Possibly related	+	±	±	?	±
Possibly unrelated	-	-	±	?	±
Definitely unrelated	-	-	-	?	+

Note: + indicates positive or yes; - indicates negative or no; ± indicates difficult to judge; ? indicates unknown.

9.3.5 Management of Adverse Events

Throughout the study, researchers will closely monitor the subject's health status, clinical symptoms and signs. If an adverse event occurs, it should be treated promptly, necessary measures should be taken, and it should be recorded in detail. Subjects without adverse events will be observed until the end of the study. At the end of the trial, if a subject still has unresolved adverse events before leaving the clinical research center, follow-up should be continued until the symptoms, signs, physical examination, laboratory tests of the adverse event return to normal or have stabilized, or the subject is lost to follow-up or refuses follow-up.

9.3.6 Serious Adverse Events

A serious adverse event (SAE) refers to an adverse medical event occurring after a subject receives the investigational product, such as death, life-threatening condition, permanent or severe disability or loss of function, subject requiring hospitalization or prolonged hospitalization, and congenital abnormality or birth defect.

(1) Death.
(2) Life-threatening: This refers to the subject being at risk of death when the adverse event occurs, not the assumption that the adverse event would lead to death if more severe.
(3) Permanent or severe disability or loss of function: The outcome of the adverse event may cause severe inconvenience or interference with the subject's normal life and activities.
(4) Requiring hospitalization or prolonged hospitalization. The following situations are not reported as SAEs:

After admission, hospitalization duration is less than 12 h;

Pre-planned admission (such as admission as part of the study process);

Hospitalization unrelated to AE (such as admission to a social welfare institution for temporary care).

(5) Congenital abnormality or birth defect: The subject's offspring has malformation or congenital functional defect.

(6) Other important medical events: Medical and scientific judgment must be used to decide whether to expedite reporting of other situations. For example, important medical events may not immediately threaten life, cause death or require hospitalization, but if medical measures are needed to prevent one of the above situations, they are usually considered serious. For example, important treatment in the emergency room or allergic bronchospasm occurring at home, non-hospitalized cachexia or convulsions, drug dependence or addiction.

Management of subjects when SAE occurs

If an SAE occurs, the subject should withdraw from the trial, and the investigator should immediately take effective management measures, provide active treatment, and protect subject safety.

Suspected unexpected serious adverse reaction (SUSAR) refers to a suspected and unexpected serious adverse reaction whose nature and severity exceed the existing information such as the investigator's brochure, the package insert of the marketed drug, or the product characteristics summary. Among them, adverse drug reaction refers to any harmful or unintended reaction to the human body that may be related to the investigational product during clinical trials. The causal relationship between the investigational product and the adverse event has at least a reasonable possibility, that is, correlation cannot be excluded.

SAE recording and reporting

If an SAE occurs, the investigator should complete the Serious Adverse Event Report Form as detailed as possible, sign and date it. The investigator should report all serious adverse events in writing to the sponsor immediately (no more than 24 h) after becoming aware of the SAE, and subsequently provide detailed written follow-up reports in a timely manner, and report to the ethics committee according to its requirements. If the SAE is assessed by the sponsor as a "suspected unexpected serious adverse reaction", it should be reported rapidly to the National Medical Products Administration review institution, clinical trial institution and ethics committee in accordance with the requirements of the Standards and Procedures for Rapid Reporting of Safety Data During Drug Clinical Trials, and to the health administrative department. The investigator should report to the ethics committee the suspected unexpected serious adverse reactions and other safety information provided by the sponsor (such as other SAE reports). For reports involving death events, the investigator should provide other required information to the sponsor and ethics committee, such as autopsy reports and final medical reports. Serious adverse event reporting channels:

Table 9: Serious Adverse Event Reporting Channels

Unit	Contact Person	Contact Information
Ethics Committee of The Affiliated Hospital of Qingdao University	Zhang Xiaolei	Fax: 0532-82912611; Tel: 0532-82912611; Email: qingyilunli@126.com
Sponsor: Qilu Pharmaceutical Co., Ltd.	Gu Xingli and "Qilu Drug Safety" mailbox	Tel: 0531-83126901; Email: xingli.gu@qilu-pharma.com and qisaemaibox@qilu-pharma.com

9.3.7 Pregnancy Event Reporting

Subjects are willing to have no pregnancy, sperm donation or egg donation plans from the time of signing informed consent (female subjects have taken effective contraceptive measures within 14 days before the first dose) until 6 months after the last dose, and voluntarily take effective contraceptive measures. Specific contraceptive measures are shown in Appendix 2.

If an enrolled female subject becomes pregnant after receiving the investigational product until 6 months after the last dose, the investigator must report the pregnancy to the sponsor. The investigator should follow up the pregnancy outcome, and any abnormal results in the mother or fetus must be reported.

If the partner of an enrolled male subject who has received the investigational product becomes pregnant (from the first receipt of the investigational product to 6 months after the last dose), with the partner's consent, the investigator should make maximum efforts to obtain information about the pregnancy process, outcome and fetal health.

When reporting pregnancy to the sponsor, the sponsor's designated reporting format must be used. The investigator should report the pregnancy event to the sponsor within 24 h of becoming aware of it.

If the pregnancy outcome is spontaneous abortion, stillbirth, medically induced abortion, fetal malformation (any congenital abnormality/birth defect/fetal growth retardation), it is considered an SAE and should be reported in writing to the sponsor immediately (no more than 24 h), and detailed written follow-up reports should be provided in a timely manner.

All neonatal deaths occurring within one month of birth, regardless of cause, should be reported as serious adverse events. In addition, for any infant death after one month of birth, as long as the investigator considers that the death may be related to the study drug, it should also be reported.

10 Data Management and Statistics

10.1 Requirements for Investigator Data Entry

Subject data on clinical sampling records should be recorded using codes. Subjects can only be identified by subject code or initials of their name.

All information required by the study protocol must be provided, and any omission must be justified. The monitor should check the completeness, accuracy and legibility of records and whether the investigator has signed.

All records on clinical sampling records must be clearly filled in with a black pen to ensure clear and legible copies. Incorrect records must be modified by drawing a horizontal line through them so that the original record remains visible, and then making the correction beside it. The modification record must be signed and dated by the investigator.

The investigator must retain the original documents of each subject participating in the trial. All information on the clinical sampling records must be derived from these original documents. The original documents should contain all demographic information and treatment information, study medical records and relevant forms recording the trial process, including laboratory test data, electrocardiograms, etc., as well as the signed informed consent indicating the trial number and trial title.

10.2 Data Management

The clinical data collection method of this trial is electronic data capture (EDC). The electronic data capture and data management work uses the Goclin V1.9.0 (or newer version) system developed by Guilin Gukelin Technology Co., Ltd.

10.2.1 Data Management Plan

The data management plan is written by the data manager. It is the guiding document for the entire data management process, and the data management process should be carried out according to established operating procedures.

10.2.2 CRF Design

Data collection forms are designed according to the trial protocol, defining the trial process, data form names and data items collected. They are finalized after review and approval by the sponsor.

10.2.3 Database Establishment and Testing

The data manager builds the database and entry interface according to the clinical trial protocol and related documents (such as study medical records), and conducts testing. The testing content includes: page design, visit period settings, consistency of data entry and output, different user access permissions, etc. After testing is completed, the electronic case report form (eCRF) is exported, reviewed and approved by the sponsor, data project manager and project statistician, finalized and put into use.

10.2.4 Data Entry

The data manager writes the eCRF completion guidelines. Investigators or clinical research coordinators (CRCs) fill in the eCRF in the EDC system in a timely, accurate, complete and standardized manner according to the eCRF completion guidelines.

10.2.5 Source Data Verification (SDV)

The clinical monitor (CRA) checks the consistency between eCRF data and source data at the clinical trial institution.

10.2.6 Data Review

The data manager reviews the completeness, logic and accuracy of the database data, using logical checks (online EDC checks) and manual checks (offline checks).

10.2.7 Queries

Suspicious data issues found during data review are sent to the investigator for clarification through query information in the database system.

10.2.8 Query Resolution

After receiving the query, the investigator or CRC clarifies and answers the suspicious data. For query data that does not need to be modified, the clarification reason must be filled in; for data that needs to be modified, data correction should be made, and the clarification reason should be noted when necessary. The data manager confirms the response to the query and may send the query again if necessary until the data is “clean”.

10.2.9 Medical Coding

Medical coding is only for enrolled subjects. Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA 26.1 or above).

10.2.10 Data Review Meeting

Before database lock, the sponsor, investigator, data manager and statistician will review the final data through meetings (including telephone conferences), review and evaluate protocol deviations or violations, divide analysis sets, and generate a data review report.

10.2.11 Database Lock and Export

After all subjects complete the trial, all data are entered into the system, and data cleaning is completed, the data manager submits a database lock application. After the data manager, project statistician, sponsor and principal investigator sign the database lock document, the data manager locks the database. After database lock, the data manager extracts data, confirms that the data is correct and complete, and delivers it to the statistical analyst. After database lock, if serious data problems are found and it is necessary to unlock the database, the data manager, project statistician, principal investigator and sponsor need to sign relevant documents for unlocking and re-locking, and re-lock the database after data correction.

10.2.12 Data Management Report

After the trial is completed, the data manager writes a data management report based on the actual project execution and process.

10.2.13 Archiving and Retention of Data and Data Management Documents

After the trial is completed, the data management unit provides the drug registration applicant with a CD containing the final version of data management-related electronic documents and the final version of the data set. Within 5 years after the trial is completed, the data management unit may open the database system according to the agreed time and process as needed.

10.3 Analysis Sets

The following analysis populations will be used for analysis of study data:

Full Analysis Set (FAS): The full analysis set includes all randomized subjects.

Safety Set (SS): The safety analysis population will include all randomized subjects who received at least one dose of the investigational product.

Pharmacokinetic Concentration Set (PKCS): All randomized subjects who received the study drug and had at least one blood drug concentration data during the trial.

Pharmacokinetic Parameter Set (PKPS): All randomized subjects who received at least one dose of the study drug and had at least one valid pharmacokinetic parameter data.

Bioequivalence Set (BES): The BES is a subset of the PKPS, used for evaluating bioequivalence between drugs. It includes subjects who have at least one period and at least one evaluable pharmacokinetic parameter (AUC0-t, AUC0-∞ and Cmax). After subjects take the drug, if the following situations occur, the pharmacokinetic data of the corresponding period should not be included in the bioequivalence evaluation:

a) Subjects enrolled with severe protocol violations that affect PK parameter results, or whose parameters cannot be estimated;

b) Subjects whose pre-dose concentration is >5% of Cmax;

c) Subjects who use concomitant medication during the trial that affects PK parameters;

d) Subjects who vomit within twice the median Tmax after taking the study drug;

e) Subjects whose first sample is Cmax and for whom early samples (5–15 min after dosing) were not collected.

10.4 Statistical Analysis

10.4.1 Statistical Analysis Software

WinNonlin® 8.2 (or above) or SAS V9.4 (or above) software will be used to calculate pharmacokinetic parameters by non-compartmental model based on actual sampling time. SAS 9.4 or above software will be used for related statistical analysis. Detailed statistical analysis methods are described in the statistical analysis plan.

10.4.2 Subject Distribution

List and describe subject screening, enrollment, and trial completion; subject withdrawal, exclusion, and whether included in analysis sets; and analysis set division.

10.4.3 Demographic Data Analysis

Descriptively analyze subject demographic data. For continuous variables, calculate the number of cases, arithmetic mean, standard deviation, quartiles, minimum and maximum; for categorical and ordinal variables, calculate frequencies and percentages.

10.4.4 Medication and Medication Compliance

List and describe subject medication, medication compliance and concomitant medication.

10.4.5 Pharmacokinetic Analysis

Use PKCS and PKPS, and use actual time for sampling time points to analyze PK blood sample data.

According to the administered formulation, list the plasma letermovir concentration and actual blood sample collection time at each blood collection time point for each subject, and perform descriptive analysis of blood drug concentrations at each time point.

Plasma concentration-time curve: Draw the plasma letermovir concentration-time curve and concentration-time semi-logarithmic curve for each subject after oral administration of the test product and reference product; and the mean concentration-time curve and mean concentration-time semi-logarithmic curve of plasma letermovir for all subjects after oral administration of the test product and reference product.

Pharmacokinetic parameters: According to actual sampling time, use non-compartmental model to calculate pharmacokinetic parameters. Calculate the pharmacokinetic parameters AUC0-t, AUC0-∞, AUC_%Extrap, Cmax, t1/2, Tmax, λz of plasma letermovir after subjects take the test product and reference product, and calculate the arithmetic mean, standard deviation, quartiles, maximum, minimum, geometric mean and coefficient of variation for each parameter.

10.4.6 Bioequivalence Analysis

Use BES. After natural logarithmic transformation of the primary pharmacokinetic parameters AUC0-t, AUC0-∞ and Cmax of letermovir, administration sequence, formulation and administration period will be treated as fixed effects, and subject individual (nested within sequence) will be treated as a random effect for analysis of variance (ANOVA). The geometric mean ratio of the test product to the reference product and its 90% confidence interval will be calculated.

The bioequivalence evaluation of the test product and reference product of letermovir tablets is based on the pharmacokinetic parameters AUC0-t, AUC0-∞ and Cmax of letermovir. When the 90% confidence intervals of the geometric mean ratios of AUC0-t, AUC0-∞ and Cmax of letermovir between the test product and the reference product do not exceed the equivalence interval of 80.00–125.00%, the two formulations are considered bioequivalent.

10.4.7 Safety Analysis

Use SS. Adverse events will be coded using MedDRA 26.1 or above. The incidence rate will be summarized according to the test product and reference product groups. All adverse events, their severity and relationship to the drug will be described in list form. Changes in vital signs, physical examination, laboratory tests (blood routine, blood biochemistry and urinalysis) and electrocardiogram results before and after the trial will be analyzed.

11 Quality Control and Quality Assurance

The sponsor and investigators should establish their own quality assurance systems, fulfill their respective responsibilities, strictly follow the clinical trial protocol, and adopt corresponding standard operating procedures to ensure the implementation of quality control and quality assurance systems for clinical trials.

11.1 Management Organization and GCP Implementation

The sponsor and investigators should use standard operating procedures to implement the quality control and quality assurance system of clinical trials.

Source documents must comply with Chinese GCP requirements.

Laboratory test results must be accurate and reliable.

All observation results and findings should be verified to ensure data reliability.

Establish a complete trial organization and clarify the responsibilities of personnel at all levels.

The principal investigator is responsible for overall quality control or entrusts a quality control officer to conduct full-process quality control and execute the responsibilities of personnel at all levels.

The principal investigator, sponsor and analytical testing unit are jointly responsible for designing the study protocol and case report form, which will be used after sponsor approval. After the trial is completed, write the final trial report.

Before the trial, all personnel participating in the trial should study the protocol and receive GCP training and obtain corresponding certificates.

Physicians and nurses participating in the trial must strictly comply with the protocol, proceed according to procedures, and must not change them arbitrarily.

Dedicated personnel are responsible for the custody of clinical sampling records, which will be submitted to the institution office for archiving after the trial is completed.

11.2 Quality Assurance of Clinical Trial Process

The clinical trial unit conducting this project must have the qualifications and capabilities to undertake drug clinical trials.

Investigators participating in clinical trials must have professional expertise, qualifications and capabilities for clinical trials, pass qualification review, and personnel requirements should be relatively fixed.

To ensure the quality of clinical trials and protect subject rights, before trial initiation, all researchers participating in the trial should receive training on the trial protocol, current GCP and

relevant standard operating procedures of the study, so that researchers have a full understanding of the clinical trial protocol and the specific connotation of each indicator. Researchers can participate in the clinical trial only after authorization by the principal investigator. During the trial, investigators should conscientiously perform clinical operations according to institutional SOPs and protocol requirements, and record truly, timely, completely and standardly.

Monitors should monitor according to GCP requirements and write monitoring reports, including: trial progress; whether the trial is proceeding as planned; storage and dispensing of investigational product; reliability of data sources, etc.

Quality control personnel conduct quality checks on the trial process and corresponding source records. After the trial is completed, the research unit organizes the corresponding project documents, and after verification by quality control personnel, archives them.

11.3 Quality Assurance of Sample Testing Process

The analytical testing laboratory undertaking the analysis should establish a quality assurance system, strictly follow domestic and international relevant technical guideline standards, laboratory standard operating procedures and quality control procedures for quality verification, formulate verification plans, and conduct verification according to the plan content. The verification content includes but is not limited to: personnel training and authorization, sample management, standard product management, instrument and equipment validation, calibration and maintenance, method validation, sample testing, data verification, etc. Laboratory quality assurance personnel conduct audits of different scopes on the analytical testing process and test results according to testing work progress and quality control personnel verification results.

11.4 Quality Assurance of Data Transfer, Calculation and Reporting

After data is entered into eCRF at the research center, quality control personnel should check the consistency between eCRF data and source records to ensure data is accurately entered into eCRF. CRA verifies 100% whether the trial data entered in the eCRF system is complete, accurate and consistent with source medical records. For data items that are questionable or inconsistent with source medical records, queries should be raised in a timely manner. And urge CRC and investigators to answer queries, verify and correct inconsistent data.

Data management department personnel use logical checks and manual checks to verify data entry quality. Questionable results are sent to investigators and CRC in the form of queries, and investigators and CRC verify and modify them. Quality control personnel verify data management documents and database data.

The sponsor may, as needed, combine trial progress and quality control personnel/monitor verification results to conduct audits of different scopes on the above clinical trial process, sample testing process, data, reports and calculation process.

12 Handling of Abnormal Situations During the Trial

12.1 Handling Principles

If unplanned abnormal situations related to this project occur during the trial, the investigator should promptly notify the sponsor and negotiate with the sponsor on how to handle the situation and obtain written authorization from the sponsor. The cause, handling method and result of the situation should be recorded in detail. If the abnormal situation violates the protocol requirements, it should be recorded as a protocol deviation.

12.2 Trial Termination Criteria

A major error in the clinical trial protocol is found during the trial, making it difficult to evaluate the drug;

The sponsor requests termination under the premise of fully protecting subject rights and safety;

The regulatory authority or ethics committee orders termination of the trial for some reason.

12.3 Risk Assessment and Risk Management

Common adverse reactions in letermovir-related clinical studies include: nausea, vomiting, diarrhea.

After administration in each period, medical staff should continuously and closely observe subjects for possible adverse events, especially signs and symptoms related to hypersensitivity, dizziness and muscle spasms that may lead to serious consequences.

12.4 Protocol Deviation or Violation

All requirements specified in the study protocol must be strictly implemented. Any intentional or unintentional behavior that deviates from or violates the trial protocol and GCP principles can be classified as protocol deviation or protocol violation. All protocol deviations or violations should be recorded promptly and accurately. If it is determined to be a deviation, and after evaluation it is considered that the deviation may affect subject safety, subject eligibility or data reliability, the project coordinator, investigator or designated personnel should report it to the ethics committee and sponsor as soon as possible; if the deviation has little or no impact on the above matters, it can be reported to the ethics committee and sponsor after the trial is completed. Before database lock, the principal investigator, data manager, statistician and sponsor will review and evaluate all protocol violations or deviations one by one to determine whether the corresponding subjects can enter a specific statistical analysis set.

13 Protocol Amendments

After this protocol is approved by the ethics committee, if it needs to be modified, a protocol amendment description must be prepared, signed by the principal investigator, and agreed by the sponsor before the protocol can be modified.

After protocol modification, it can be implemented only after approval by the sponsor and ethics committee.

14 Ethical Standards and Informed Consent

14.1 Ethical Standards

This clinical trial must comply with the Declaration of Helsinki, the Good Clinical Practice (GCP) promulgated by NMPA, and relevant regulations. Before the trial begins, ethics committee approval must be obtained before this study can start. During the clinical study, any modification to the trial protocol must be approved or filed with the ethics committee again. The investigator is responsible for submitting interim reports to the ethics committee according to its requirements, and should notify the ethics committee that the trial has ended after the trial is completed.

14.2 Informed Consent

Subjects must sign the informed consent for this trial before receiving screening to protect their legitimate rights and interests. The investigator is responsible for fully and comprehensively introducing the purpose of the study, the study method, the effects of the drug, reasonable expected benefits, possible toxic and side effects and possible risks to subjects. Subjects should be informed of their rights, the risks and benefits they will bear, and any new information about the investigational product should be promptly communicated to subjects. Subjects should be informed that this clinical trial is completely voluntary, and subjects can withdraw from the trial unconditionally at any time during the trial, and subjects will not be punished for withdrawing from the trial. Subjects should be informed that information about their participation in the study will be strictly confidential, but the research party, sponsor and relevant national regulatory authorities have the right to read, store and statistically process the subject's trial data in accordance with relevant regulations. The informed consent form should indicate the version number and version date. Only subjects who fully understand the risks and benefits of this clinical trial, as well as potential adverse events, and sign their name and date on the informed consent form can participate in this clinical trial. The informed consent form is in duplicate. The investigator will give one copy signed and dated to the subject and keep one copy in the subject's file.

15 Archiving of Materials

To ensure the evaluation and supervision of clinical research by the National Medical Products Administration and the sponsor, the investigator agrees to keep all study materials, including original records of subject hospitalization, informed consent forms, detailed records of drug dispensing, etc. Paper and electronic documents generated by clinical trial institutions and sample testing laboratories should be properly preserved to ensure timely traceability. For clinical trials used to apply for drug registration, essential documents should be kept at least until 5 years after the investigational drug is approved for marketing; for clinical trials not used to apply for drug registration, essential documents should be kept at least until 5 years after the clinical trial is terminated. All materials of this clinical study are owned by Qilu Pharmaceutical Co., Ltd. Without prior written agreement between the investigator and the sponsor, documents at the research center must not be damaged. If the investigator chooses to provide trial documents to another party or transfer them elsewhere, the sponsor must be notified. Except as required by the National Medical Products Administration, the investigator may not provide them to third parties in any form without the written consent of the sponsor.

16 References

[1] CDE. Technical Review Report for Marketing Application of Letermovir Tablets (JXHS2000165-166).
[2] CDE. Package Insert of Letermovir Tablets (JXHS2000165-165).
[3] FDA. PREVYMIS™ (letermovir) tablets, for oral use. Initial U.S. Revised: 03/2020.
[4] FDA. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S). APPLICATION NUMBER: 209939Orig1s000 209940Orig1s000.
[5] PMDA. Package Insert of Letermovir Tablets. January 2022.

Appendix 1 Clinical Laboratory Tests
Blood Biochemistry Blood Routine
At screening, end of study or early termination, the following items will be tested:
Total protein
Albumin
Globulin
Total bilirubin
Direct bilirubin
Alanine aminotransferase
Aspartate aminotransferase
γ-Glutamyl transferase
Alkaline phosphatase
Triglycerides
Total cholesterol
Glucose
Urea
Creatinine
Uric acid At screening, end of study or early termination, the following items will be tested:
White blood cell count
Neutrophil percentage
Lymphocyte percentage
Monocyte percentage
Eosinophil percentage
Basophil percentage
Neutrophil count
Lymphocyte count
Monocyte count
Eosinophil count
Basophil count
Red blood cell count
Hemoglobin
Platelet count
Infectious Disease Screening Only at screening; results within 21 days before the first dose may be accepted:
Hepatitis B surface antigen
Hepatitis C antibody

HIV antibody
Treponema pallidum antibody
Urinalysis At screening, end of study or early termination, the following items will be tested:
Occult blood
Protein
Glucose
pH
Specific gravity
Ketones
Bilirubin
Urobilinogen
White blood cell count
Red blood cell count
Urine Drug Screening At screening and at admission in each period:
Morphine
Methamphetamine
Ketamine
Methylenedioxymethamphetamine
Tetrahydrocannabinol acid
Pregnancy Test (female only) Female subjects will undergo urine pregnancy test at screening, and blood pregnancy test at admission and end of study/early termination:
Human chorionic gonadotropin (β-HCG)
Appendix 2 Contraceptive Measures and Requirements
1. Female Subjects
Before enrollment, female subjects of childbearing potential must have a negative pregnancy test at screening, and the pregnancy test must also be negative at admission in each period.

From 14 days before the first dose until the end of the trial, subjects must also agree to one of the following:

Complete abstinence.

Correct use of condoms by male partners.

Correct use of one of the following contraceptive methods:

Intrauterine device (IUD) with an annual failure rate <1%

Female barrier method: cervical cap or diaphragm with spermicide

Tubal sterilization

From the end of the trial until 6 months after the last dose, in addition to the above contraceptive measures, subjects may also use the following contraceptive measures:

Hormonal contraceptives

Levonorgestrel implant

Progesterone injection

Oral contraceptives (combined or progesterone-only)

Vaginal contraceptive ring

Transdermal contraceptive patch

2. Male Subjects
Male subjects must agree to avoid donating sperm to women from the time of signing informed consent until 6 months after the last dose.

3. Procedures to Follow in Case of Pregnancy
If a subject (or their partner) becomes pregnant at any time during the study, or if a subject becomes pregnant within 6 months after the last dose (male subject's partner becomes pregnant within 6 months), the subject will be required to notify the investigator.