Clinical Trial Protocol

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase II/III Clinical Study to Evaluate the Efficacy and Safety of Orally Administered GST-HG171 Plus Ritonavir in Patients with Mild/Moderate COVID-19

Protocol No.: GST-HG171-II/III-01

Version: Version 1.5

Date: February 27, 2023

Sponsor: Fujian Akeylink Biotechnology Co., Ltd.

PROTOCOL SIGNATURE PAGE-SPONSOR

I agree:

- To conduct this trial in strict compliance with the protocol, the *Declaration of Helsinki*, the current International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the GCP Guidelines of (China) National Medicinal Products Administration (NMPA), and other applicable regulations and guidelines.
- To be responsible for initiating, applying for, organizing and sponsoring this clinical trial, and auditing of the clinical trial implementation.

I have read the full text of this protocol and agreed on all the contents.

Responsible Person of the Sponsor	Tianxiang Zhang	Position	Director of Department of Medicall Affairs	
Signature	Tianxiang Zhang	Date	27/2. 2023	
Company Name	Fujian Akeylink Biotechnology Co., Ltd.			
Contact Address	Building 16, Phase II, Innovation Park, No. 7, Wulong Jiangzhong Avenue, High-tech Zone, Fuzhou, Fujian		Post Code	350108
Telephone	+86-13247651892			

PROTOCOL SIGNATURE PAGE-INVESTIGATOR

I agree:

- To conduct this trial in strict compliance with the protocol, the *Declaration of Helsinki*, the current International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the GCP Guidelines of (China) National Medicinal Products Administration (NMPA), and other applicable regulations and guidelines.
- To keep all materials and information provided by the sponsor according to confidentiality requirements, and clearly mark that the information is confidential when it is submitted to the Ethics Committee (EC).

I have read the full text of this protocol and agreed on all the provisions listed in the protocol.

Principal Investigator	Nanshan Zhong	Position	Director of National Clinical Research Center for Respiratory Diseases	
Signature		Date	Feb. 27, 2023	
Leading Site of Clinical Study	The First Affiliated Hospital of Guangzhou Medical University			
Contact Address	No. 28, Qiaozhong Middle Road, Liwan District, Guangzhou, Guangdong		Post Code	510160
Telephone	-			

PROTOCOL SIGNATURE PAGE-INVESTIGATOR

I agree:

- To conduct this trial in strict compliance with the protocol, the *Declaration of Helsinki*, the current International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the GCP Guidelines of (China) National Medicinal Products Administration (NMPA), and other applicable regulations and guidelines.
- To keep all materials and information provided by the sponsor according to confidentiality requirements, and clearly mark that the information is confidential when it is submitted to the Ethics Committee (EC).

I have read the full text of this protocol and agreed on all the provisions listed in the protocol.

Principal Investigator	Hongzhou Lu	Position	President
Signature	Hongzhou Lu	Date	Dec 12, 2022
Leading Site of Clinical Study	The Third People's Hospital of Shenzhen		
Contact Address	No. 29, Bulan Road, Longgang District, Shenzhen, Guangdong	Post Code	518112
Telephone	-		

SIGNATURE PAGE-STATISTICAL ANALYSIS INSTITUTION

I agree:

- To perform the duties of statistical analysts in strict accordance with the protocol, the *Declaration of Helsinki*, the current International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the GCP Guidelines of (China) National Medical Products Administration (NMPA), the *Technical Guidelines for Clinical Trial Data Management*, the *Technical Guidelines for Electronic Data Collection in Clinical Trials*, the *Guidelines for Planning and Reporting of Drug Clinical Trial Data Management and Statistical Analysis*, the *Guidelines for Biostatistics of Drug Clinical Trials*, and other relevant regulations and guidelines.
- To properly store all the materials and information provided by the sponsor according to confidentiality requirements.

I have read the full text of this protocol and agreed on all the provisions listed in the protocol.

Statistician	Zhuhua Lin	Position	Senior Statistician	
Signature	Zhuhua Lin	Date	27Feb 2023	
Company Name	MacroStat (China) Clinical Research Co., Ltd.			
Contact Address	Floor 8-9, No. 232, Liangjing Road, Pudong New Area, Shanghai		Post Code	201203
Telephone	+86-21-50276030			

PROTOCOL SIGNATURE PAGE OF SUB-SITES

(Clinical Study Site)

We have read and confirmed this protocol. We agree to conduct this trial in strict compliance with the protocol, the *Declaration of Helsinki*, the current International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the GCP Guidelines of (China) National Medicinal Products Administration (NMPA), and other applicable regulations and guidelines.

Principal Investigator		Position		
Signature		Date		
Clinical Study Site				
Contact Address			Post Code	
Telephone				

PROTOCOL REVISION RECORD

Protocol/Amendment No.	Version	Version Date	Main Revisions
GST-HG171-II/III-01	Version 1.0	November 15, 2022	Not applicable
GST-HG171-II/III-01	Version 1.3	December 10, 2022	1. Study Title: "Double-Dummy" was deleted. 2. The power of the study was increased from 85% to 90%, and thus the sample size will increase to 1200 subjects. 3. Observation of the preliminary efficacy during the data review of the sentinel cohort was added, and the safety review of the sentinel cohort was designated as the first interim analysis and supplemented with descriptions in the relevant chapters of the interim analysis. The interim analysis in the original protocol was changed to the second interim analysis accordingly. 4. Inclusion criteria: Positive RT-PCR test in nasopharyngeal swabs or oropharyngeal swabs and other specimens within "5 days" before randomization was changed to "4 days", and the "first" positive result was required within 4 days before randomization. Accordingly, the screening period was revised to 4 days. 5. Inclusion criteria: The time of the first onset of COVID-19 symptoms was changed to "within 48 hours before randomization", the number of target symptoms of COVID-19 in the designated COVID-19 symptoms and efficacy endpoints was changed from 5 to 11, and "headache, muscle or body aches, diarrhoea, chills, nausea, vomiting" with at least 2 designated COVID-19 symptoms were added under the target symptoms. In addition, requirements of "including at least one designated symptom: fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing" and "RT-PCR result of N gene or ORF gene of SARS-CoV-2 within 48 hours before randomization shows a Ct value of < 35" were added to the inclusion criteria. 6. "Time to sustained recovery of fever and respiratory symptoms within 28 days after treatment" was added as a key secondary

			efficacy endpoint. 7. Requirements for contraceptive measures: from "during the whole study period or for at least 14 days after the last dose (whichever is longer)" to "throughout the whole study period and for 28 days after the end of the study". 8. In exclusion criteria: Refined the description of acute systemic infection: "For example, the pathogen detection indicates that it is complicated with influenza; there is a high possibility of bacterial infection as indicated by symptoms, signs, laboratory tests or imaging". 9. Added the distinction between withdrawal from treatment and withdrawal from the study, and specified that "except for withdrawal of informed consent or lost to follow-up, the subjects who early withdraw from treatment are encouraged to stay in the study as much as possible, participate in the visit according to the time point specified in the Schedule of Activities, and allow to collect relevant data, but it was ultimately up to the subject to decide whether to withdraw from the study". In addition, "according to the investigator's judgment, the subject had poor efficacy" and "the subject had progressed to severe/critical COVID-19" were added to the withdrawal criteria. 10. "Ritonavir tablet placebo" was changed to "Ritonavir blank tablet". 11. "Short-acting acetaminophen" was changed to "short-acting single-ingredient acetaminophen", and the maximum permitted dose was changed from 2000 mg to 3000 mg. 12. "The boundary value generated by the Lan-DeMets spending function method to approximate O'Brien-Fleming will be used to control type I errors ($\alpha < 0.05$ for a two-sided test)" was added in the statistical analysis section. 13. Modification of intercurrent events and handling strategies: apply composite variable strategy for using prohibited medications or therapies; "concomitant

			drug" was replaced with "concomitant drug other than prohibited medications or therapies"; in the case of early discontinuation of treatment due to AE/early withdrawal of treatment due to poor medication compliance (< 80%), the treatment policy strategy is applied; “In the case that a patient has progressed to severe/critical COVID-19 or has an investigator-assessed poor efficacy, the composite variable strategy is applied” was added; deleted new influenza infections; added delay or interruption of administration due to AE (using treatment policy strategy) and death (using composite variable strategy). 14. "The time to sustained recovery of clinical symptoms will be compared between the two groups of subjects using the log-rank test adjusted for randomization factors" was added in the population-level summary. 15. Interim analysis: detailed description of unblinded sample size re-estimation/futility analysis was added, "If the test result of the efficacy difference between the treatment group and the control group reaches the statistical significance criterion (< two-sided of 0.003), the superiority of the treatment group can be supported and the possibility of communicating with the regulatory authority about the early application can be prompted; the final analysis will be performed when the original target number of events is reached (α will be recovered, and the significance criterion is two-sided of 0.05)" was removed from DSMB recommendation. Type I error spending calculations for two interim analyses was added. 16. Study procedures: C-reactive protein (CRP) was added to the laboratory tests during the screening period; "After the subject is discharged from the hospital, no sampling is required; if the subject receives a qualitative nucleic acid test due to the requirements of the epidemic prevention department or for other reasons, then record the test results in the subject's diary card" was added under the qualitative nucleic

			acid test; "After the subject is discharged from the hospital, no sampling is required" was added under the quantitative nucleic acid test; "For subjects with baseline imaging findings of pneumonia, reassessment is performed on D7 as a secondary efficacy endpoint; for subjects without baseline imaging findings of pneumonia, reassessment is not required on D7; Changes on D7 relative to baseline, including no change, deterioration, and improvement should be assessed by the investigator" was added; blood sample collection within 2 h before D1 administration for PopPK sampling was added; each PopPK blood collection point was clearly defined as before/after the first administration of the day; the subject's diary card was changed to "Subject diary cards will be dispensed at visit on D1 and collected at the last visit; if the subject is discharged during this period, the diary card dispensed on D1 will be collected at discharge and a new subject diary card will be dispensed."; "the subjects should collect nasopharyngeal swabs by themselves and send nucleic acid samples to the central laboratory for testing" was deleted for telemedicine visits. 17. "4.3.13 Discharge During the Study" was added. 18. The results of Phase I studies were supplemented in 1.3.4 Clinical Studies. 19. The rationale of placebo control and dose selection was supplemented in 1.4 Scientific Rationale for Study Design. 20. "Adverse medical events that are considered by the investigator to be COVID-19 complications or COVID-19-related progresses do not need to be recorded as AEs" was added under the AE Collection. 21. A sensitivity analysis and a supplementary analysis for the efficacy analysis were added. 22. Subgroup analysis was added.
GST-HG171-II/III-01	Version 1.4	January 3, 2023	1. Except in citing the guidances and guidelines, etc., according to the latest announcement of the National Health

			Commission, the Chinese name of COVID-19 in the title was changed (Only applicable to Chinese version)". 2. As it is confirmed that this study will only be conducted in China, the text "international" in "international multicenter" in the title was removed, and the randomization stratification factor "region [China/Southeast Asia]" was removed at the same time. 3. The Chinese name of the leading study site the First Affiliated Hospital of Guangzhou Medical University was corrected (Only applicable to Chinese version). 4. Inclusion criteria 2: Positive RT-PCR test in nasopharyngeal swabs or oropharyngeal swabs within "4 days" before randomization was changed to "5 days". Accordingly, the duration of the screening period was changed to 5 days and the duration of study to 33 days. 5. Inclusion criterion 3: the time of first appearance of COVID-19 symptoms was changed to within 72 hours before randomization. 6. In inclusion criterion 4, "serum pregnancy test" was changed to "urine pregnancy test". 7. "Hepatitis B virus surface antigen (HBsAg) positive" and “hepatitis C virus antibody (Anti-HCV) positive and HCV-RNA positive" in exclusion criterion 4 were deleted; "and" in " treponema pallidum antibody (TP-PA) positive and rapid plasma reagin (RPR) positive for syphilis" was changed to "or". The Schedule of Activities was modified accordingly, and "Specific test items can be selected or adjusted according to the testing capability of the study site" was added. 8. The indicator for assessing renal function in the exclusion criteria was changed from glomerular filtration rate to serum creatinine level. 9. Concomitant medications: Appendix 8 Medication Guide for Symptom alleviation During the Study was added. 10. "Rescue treatment" was changed to "symptomatic treatment", and the relevant text was modified according to Appendix 8:

			"Recovery of COVID-19-related symptoms is the primary endpoint of this study. If the relevant symptoms in the subject are mild, no intervention is required unless necessary, and it is recommended to observe the symptoms for 1-2 days first; if the subject remains intolerable and strongly requests medication, drug intervention can be considered as described in Appendix 8, but should be avoided whenever possible. If any medication for symptomatic treatment is used, the dosage, date and time of each dose should be recorded. Measurement of body temperature and assessment of COVID-19 symptoms will be performed before or more than 4 hours after symptomatic treatment". 11. In key secondary efficacy endpoint, "Day 5" in " change in viral load from baseline on Day 5 after treatment" was changed to "Day 4". 12. In note to key secondary efficacy endpoint 2, "sustained recovery of clinical symptoms" was changed to "sustained recovery of fever and respiratory symptoms", for consistency with the description of the endpoint. 13. The original secondary efficacy endpoint 8 "time to negative conversion of SARS-CoV-2 nucleic acid within 28 days after treatment" was changed to key secondary efficacy endpoint 3. 14. Added "non-positive influenza virus" as a requirement for inclusion in mITT and the target population for the primary estimand; with regard to mITT, indicated that "Baseline SARS-CoV-2 nucleic acid test is defined as the test result before D1 treatment; if there was no sampling on D1, the test result obtained at the time that is the closest to D1 during the screening period would be used as the baseline." 15. In sensitivity analysis, changed "taking…condition of clinical improvement and time to sustained recovery of clinical symptoms of subjects as dependent variables" to "taking…condition of and time to sustained recovery of clinical symptoms of subjects as dependent

			variables". 16. Removed listing of "significant AEs" in safety analysis. 17. In interim analysis, added "the specifics of sample size re-estimation will be provided in the interim analysis plan, and an unblinded team will be established to draft the interim analysis plan and complete the interim analysis tasks"; added "otherwise continue the trial with the original planned sample size" to the suggestions of the DSMB; changed consumption of type I error to two-sided. 18. Added "gender" and removed "China vs. outside China" in subgroup analysis. 19. Schedule of Activities: removed "admission" in "screening period/admission"; physical examination and vital signs: removed D2, D3, and D5; removed D3, D5 and added D4 for 12-lead ECG; changed serum pregnancy test to urine pregnancy test, added "during the study period, the serum pregnancy test may be added at the investigator's discretion"; removed requirement of "sampling before administration" for qualitative and quantitative nucleic acid tests, and removed D3 and D5 tests; added screening period test for quantitative nucleic acid test, and added specification of baseline; laboratory tests: removed D5 and added D4; removed CRP in "CD3/CD4/CD8, procalcitonin, erythrocyte sedimentation rate, CRP and IL-6", only retaining CRP in "laboratory tests", and removed D5 and added D4; removed D1 influenza virus test and the note; changed acceptable time of chest CT to " chest CT within 5 days before receiving the first dose is acceptable, and may not be repeated on D1"; modified requirement for PK sampling to "PK blood samples may be collected based on the subject's willingness". The collection time points include: within 2 hours before the first dose on D1, 0.5-1.5 hours after the first dose on D1, and within 2 hours before the first dose on D4. Sampling can be performed as appropriate for the actual situation. It is encouraged to at least collect

			the blood sample within 2 hours before the first dose on D4. If the PK blood sample is not collected , it may not be regarded as a protocol deviation"; added "If it is a telemedicine visit, the investigator is to instruct the subject to complete it via telephone" to COVID-19 scoring; changed "after the subject is discharged" to "in case of telemedicine" in all the notes; with regard to dispensing of subject diary card, removed "if the subject is discharged during this period, the diary card dispensed on D1 will be collected at discharge and a new subject diary card will be dispensed"; changed both "the same calendar day" and "the same day" in "the screening procedures can be completed on the same calendar day as the randomization and first administration". If screening and randomization are completed on the same day, the study assessments do not need to be repeated to "24 hours", and changed "study assessments" to "D1 study assessments"; changed "if the patient is discharged during the post-treatment assessment period" to "if the patient cannot return to the study site for on-site visit during the post-treatment assessment period". Updated the corresponding contents in Section 4.3 and Section 7 accordingly. 20. Changed "fasting blood glucose" in Appendix 6 Clinical Laboratory Tests to "blood glucose".
GST-HG171-II/III-01	Version 1.5	February 27, 2023	1. As *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 9)* was updated to *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 10)*, its document name was changed accordingly in the protocol, the Chinese translation of moderate COVID-19 was revised, and the full Chinese name of COVID was modified as Corona Virus Disease 2019 (only applicable to Chinese version). Other *Diagnosis and Treatment Protocol* related content was amended in the full text (including Appendix 7). 2. Exclusion criteria: In criterion 9, "Any comorbidity requiring surgery within 14

			days prior to randomization, or any life-threatening comorbidity within 30 days prior to randomization as determined by the investigator" was changed to "Any comorbidity requiring surgery within 14 days prior to randomization or during the study, or any life-threatening comorbidity within 30 days prior to randomization as determined by the investigator"; in criterion 13, "Subjects who have received any COVID-19 vaccine within 3 months prior to randomization" was changed to "Subjects who have received any COVID-19 vaccine within 28 days prior to randomization or planned to receive any COVID-19 vaccine during the study". 3. In Sections of Exclusion Criteria and Concomitant Medications, human immunoglobulin for intravenous injection was added as a prohibited drug; in addition to Paxlovid and Molnupiravir, Azvudine, Simnotrelvir Tablets/Ritonavir Tablets, and Deuremidevir Hydrobromide Tablets were added for antiviral therapies against SARS-CoV-2; the description of prohibited metabolic enzymes and transporter-related substrates/inducers were adjusted. 4. Node of the second interim analysis: "50% of the subjects complete the D28 assessment" was revised to "60% of the subjects complete the D28 assessment", and the corresponding consumption of type I error was modified. 5. Concomitant events: "prohibited medications or therapies" was revised to "prohibited medications or therapies that affect the efficacy endpoints". 6. Subgroup analysis: "age (≤ 60 years vs. 60-75 years vs. > 75 years)" was revised to "age (≤ 65 years vs. 65-75 years vs. > 75 years)". 7. Schedule of Activities: the time window during the screening period was adjusted from D-5 ~ D-1 to D-5 ~ D1; The randomization time was extended to the screening period; the note for telemedicine visit on D2/D3/D5 was added; "inspired oxygen flow, fraction of inspired oxygen (FiO_2) (if applicable), mode of oxygen

			delivery (if applicable), and oxygen support procedures" was revised and improved to "inspired oxygen flow (if applicable), fraction of inspired oxygen (FiO_2) (if applicable), mode of oxygen delivery (if applicable), and oxygen support procedures (if applicable)"; for 12-lead ECG, "ECG should be performed after the first dose on D1, and the recommended time window is 0.5-1.5 h after administration. ECG at subsequent visits can be conducted according to the willingness of the subject and as assessed by the investigator without specific requirements. Based on the results of the second interim analysis, a determination can be made as to whether the subsequent subjects enrolled need to continue the ECG." was added; the definition of confirmed negative conversion of nucleic acid tests was added and the description of qualitative nucleic acid test under telemedicine visit was adjusted; the description of quantitative nucleic acid test on D21 was adjusted; the description of virus strain typing test was adjusted; the description that there is no need for visits to be repeated when screening period and D1 are on the same natural day was adjusted; the time limit of assessment required to be completed prior to D1 dosing is defined as "prior to the first dose". Updated the corresponding contents in Section 4.3 and Section 7.2 accordingly. 8. Deleted the description of "relevant assessments should be completed before administration" for D1 to D5 in Section 4.3. 9. Correction of general information of study drugs: The description of ritonavir blank tablets was modified to tablets scored "RTV" on one side, and the modification was made for Ritonavir tablets simultaneously. 10. Supplementary description of Method of Administration: The interval time window of study drug administration is 12 h ± 4 h. Drug administration is not affected by meals. If one dose is delayed, it should be taken as soon as possible, but not later than 4 hours before the next dose. If less than 4

			hours before the next dose, the drug should not be taken, and the dose should be recorded as missing. The subject should not double the next dose of study drug to make up for the "missing dose". 11. Correction of drug overdose: "the dose exceeds the maximum recommended dose specified in the protocol" was revised to "the dose exceeds the dispensed dose during the study". 12. Supplementary description of Appendix 1: Body temperature is measured under the armpit. 13. Supplementary description of Appendix 2: If a patient is hospitalized for other reasons such as convenience of observation and management, an inpatient status cannot be recorded. Inpatient status can only be recorded until there is a disease progression or the severity of the condition meets the hospitalization criteria as assessed by the investigator. 14. Correction of Appendix 4: The Chinese name of rosuvastatin was revised (only applicable to Chinese version)

Clinical Trial Management Institution or Participating Parties

Sponsor

Company Name	Fujian Akeylink Biotechnology Co., Ltd.		
Project Leader	Yanan Tang	Position	Director of Department of Clinical Affairs
Contact Address	Building 16, Phase II, Innovation Park, No. 7, Wulong Jiangzhong Avenue, High-tech Zone, Fuzhou, Fujian	Post Code	350108
Telephone	-	Mobile	+86-13585734994
Fax	-	E-mail	tangyanan@cosunter.com

Contract Research Organization

Company Name	Hangzhou Tigermed Consulting Co., Ltd.		
Project Leader	Lisha Mu	Position	Project Manager
Contact Address	Room 2001-2010, Floor 20, Building 8, No. 19, Jugong Road, Xixing Street, Binjiang District, Hangzhou, Zhejiang	Post Code	310000
Telephone	-	Mobile	15032833911
Fax	-	E-mail	lisha.mu@tigermedgrp.com

Data Management

Company Name	Jiaxing Tigermed Data Management Co., Ltd.		
Project Leader	Xuefang Shao	Position	Data Manager
Contact Address	No. 28, Huixin Road, Nanhu District, Jiaxing, Zhejiang	Post Code	314001
Telephone	+86-0573-89979998-8167	Mobile	15857373144
Fax	-	E-mail	xuefang.shao@tigermedgrp.com

Statistical Analysis Institution

Company Name	MacroStat (China) Clinical Research Co., Ltd.		
Project Leader	Zhuhua Lin	Position	Senior Statistician
Contact Address	Floor 8-9, No. 232, Liangjing Road, Pudong New Area, Shanghai	Post Code	201203
Telephone	+86-21-50276030	Mobile	18818273672
Fax	+86-21-50807377	E-mail	Ella.Lin@tigermedgrp.com

Sample Testing Institution

Company Name	Teddy Clinical Research Laboratory (Wuxi) Limited		
Project Leader	Shanming Zhang	Position	Laboratory Manager
Contact Address	Floor 1, Building A, Xingye Building, No. 97, Linghu Avenue, Xinwu District, Wuxi	Post Code	214028
Telephone	0510-81999870	Mobile	+86-13774253694
Fax	0510-81999871	E-mail	shanming.zhang@teddylaboratory.com

PROTOCOL SYNOPSIS

Protocol No.	GST-HG171-II/III-01
Protocol Title	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase II/III Clinical Study to Evaluate the Efficacy and Safety of Orally Administered GST-HG171 Plus Ritonavir in Patients with Mild/Moderate COVID-19
Version No./Date	V1.5/February 27, 2023
Sponsor	Fujian Akeylink Biotechnology Co., Ltd.
Phase of the Trial	Phase II/III
Indication	Mild/moderate COVID-19
Study Objectives	1. To evaluate the efficacy of GST-HG171 plus ritonavir compared to placebo in the treatment of mild/moderate COVID-19. 2. To evaluate the safety of GST-HG171 plus ritonavir compared to placebo in the treatment of mild/moderate COVID-19. 3. To assess the population pharmacokinetic (PopPK) characteristics of GST-HG171 plus ritonavir in adult patients with mild/moderate COVID-19.
Study Design	This is a multicenter, randomized, double-blind, placebo-controlled Phase II/III clinical study to evaluate the efficacy and safety of GST-HG171 plus ritonavir in the treatment of mild/moderate COVID-19 in adult patients. In the study, 1200 adult patients with mild/moderate COVID-19 are planned to be enrolled (including patients who are at a high risk of progression to severe illness), and randomized into the investigational drug group or the placebo group in a 1:1 ratio (randomization stratification factors include presence of a high-risk factor of progression to severe illness, and COVID-19 vaccination status [incomplete basic immunization, completed basic immunization, completed booster immunization]). Subjects in the investigational drug group will be administered with GST-HG171 (150 mg/time, twice daily [BID]) plus ritonavir (100 mg/time, BID) and subjects in the placebo group will receive placebo for GST-HG171 plus ritonavir blank tablet for 5 consecutive days to assess the efficacy and safety of GST-HG171 plus ritonavir compared to placebo in the treatment of mild/moderate COVID-19 in adult patients. An independent Data and Safety Monitoring Board (DSMB) will be established in this study to assess the efficacy and safety data of study treatment given to the subjects. The study includes a sentinel cohort which consists of approximately the first 100 subjects. Unblinded safety data will be reviewed and preliminary efficacy (first interim analysis) will be observed by the DSMB when subjects in the sentinel cohort have completed investigational drug treatment and the visit assessment at Day 10 (D10). Enrollment of subjects will be continued during the DSMB review of sentinel cohort data, but the study may be suspended or terminated as recommended by the DSMB. The second interim analysis is expected to be conducted by an independent statistician when about 60% of the subjects complete the D28 assessment, and the results of this analysis will be submitted to the DSMB for review to provide a recommendation on whether to adjust the sample size, terminate or proceed the study.
Total Number of Subjects	A total of 1200 adult patients with mild/moderate COVID-19 (including patients who are at a high risk of progression to severe illness) are planned to be enrolled and are

	randomized in a ratio of 1:1, with 600 each in the investigational drug group and the placebo group.
Number of Study Sites	Approximately 50 sites.
Study Duration	The study duration for each subject is up to 33 days (including up to 5 days for screening period, and 28 days for treatment period and post-treatment assessment period).
Subject Selection Criteria	**Inclusion Criteria:** 1) Male or female subjects aged ≥ 18 years when signing the informed consent form (ICF); 2) Subjects with reverse transcription-polymerase chain reaction (RT-PCR) test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in specimens such as nasopharyngeal swabs/oropharyngeal swabs for the first time within 5 days prior to randomization, who meet the diagnostic and treatment criteria for mild and moderate cases in the *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 10)* issued by the National Health Commission of the Peoples Republic of China (see Appendix 7); 3) RT-PCR result of N gene or ORF gene of SARS-CoV-2 within 48 hours before randomization shows a Ct value of < 35; at least 2 COVID-19 target symptoms appeared for the first time within 72 hours before randomization (COVID-19 target symptoms include fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, and vomiting), including at least one designated symptom: fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing; 4) Women of childbearing potential (see Appendix 3 for the definition of "women of childbearing potential") must have a negative urine pregnancy test during the screening period. Subjects should take effective contraceptive measures throughout the study period since signing the informed consent form and for 28 days after the end of the study (see Appendix 3); 5) Subjects who are able to understand the study procedures and methods, and voluntarily participate in the study and sign the ICF after being fully informed. **Exclusion Criteria:** 1) Subjects who are known to have hypersensitivity to any component of the investigational drug; 2) Subjects who meet diagnostic and treatment criteria for severe and critical cases in the *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 10)* issued by National Health Commission of the People's Republic of China (see Appendix 7); 3) Abnormal hepatic function at screening: total bilirubin ≥ 1.5 × upper limit of normal (ULN); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × ULN; 4) Human immunodeficiency virus (HIV) antibody positive, treponema pallidum-specific antibody (TP-PA) positive or rapid plasma reagin (RPR) positive for syphilis at screening; 5) Abnormal renal function at screening: serum creatinine ≥ 1.5 × ULN; 6) Subjects with impaired immune system (including those treated with corticosteroids or other immunosuppressants, or those with progression or

	recurrence of cancer) at screening; *Note: *Patients using skin preparations are allowed to be enrolled, but the skin preparations cannot be used in the eyes, nose or ears or by inhalation.* 7) Acute onset of chronic respiratory diseases, including bronchial asthma and chronic obstructive pulmonary disease at screening; 8) There are suspected or confirmed acute systemic infections except for COVID-19 at the time of screening (for example, the pathogen detection indicates that it is complicated with influenza; there is a high possibility of bacterial infection as indicated by symptoms, signs, laboratory tests or imaging), which may interfere with the assessment of response to study intervention; 9) Any comorbidity requiring surgery within 14 days prior to randomization or during the study, or any life-threatening comorbidity within 30 days prior to randomization as determined by the investigator; 10) Subjects who are receiving HIV antiviral treatment at screening; 11) Treatment with SARS-CoV-2 antiviral drugs within 14 days prior to randomization; 12) Subjects who have received (within 30 days prior to randomization or within 5 drug half-lives, whichever is longer) or are expected to receive SARS-CoV-2 monoclonal antibody, intravenous injection of COVID-19 human immunoglobulin, or COVID-19 convalescent plasma therapy; 13) Subjects who have received any COVID-19 vaccine within 28 days prior to randomization or planned to receive any COVID-19 vaccine during the study; 14) Any drug prohibited by the package insert of Paxlovid that is currently used or expected to be used during treatment and within 4 days after the last dose of study drug, or any other drug or substance (Appendix 4) that is highly dependent on cytochrome P450 (CYP) 3A4, CYP2B6, CYP1A2, multidrug resistance gene 1 (MDR1) or organic anion transporting polypeptide (OATP) 1B3 for clearance; any potent CYP3A4 or MDR1 inducers used within 28 days prior to randomization or expected to be used during treatment and within 4 days after the last dose of study drug (Appendix 4); 15) Pregnant or lactating women; 16) Subjects who have participated in other clinical trials within 3 months prior to administration or are receiving other investigational drugs; 17) Subjects with other conditions that, in the judgment of the investigator, make them unsuitable for participation in this study. **Criteria for Subject Withdrawal** Subjects can withdraw from the study at any time during the study without giving any reason and will not be discriminated or revenged due to withdrawal from the study, without prejudice to their normal medical services. During the study, the withdrawal of subjects from treatment includes but is not limited to: 1) Subjects withdraw the ICF and voluntarily ask to withdraw from the study; 2) Subjects experience intolerable adverse events (AEs), as judged by the investigator; 3) Subjects have poor compliance, which seriously affects the implementation of the clinical trial or the evaluation of clinical efficacy and/or safety, at the discretion of the investigator; 4) According to the investigator's judgment, the subject had poor efficacy;

	5) The subject had progressed to severe/critical COVID-19; 6) Subjects stop receiving examinations or tests and are lost to follow-up (dropout) although they do not explicitly express their intention to withdraw from the study. Except for the withdrawal of informed consent or loss to follow-up, the subjects who early withdraw from treatment are encouraged to stay in the study as much as possible, participate in the visit according to the time point specified in the Schedule of Activities, and allow to collect relevant data, but it was ultimately up to the subject to decide whether to withdraw from the study. **Criteria for Study Termination** Reasons for the early termination of the study or the closure of the study site include but are not limited to: 1) New information leads to an unfavorable risk-benefit profile of the investigational drug, for example: a. The investigational drug lacks efficacy, either in this study or in other studies; b. Significant previously unknown adverse reactions or known adverse reactions with unexpected high severity/incidence; c. Other adverse safety findings, including clinical examination and non-clinical manifestations. 2) The Sponsor considers that it is unreasonable to continue the aforesaid study due to medical, ethical or commercial reasons; 3) The difficulty in enrolling subjects makes it unlikely to complete the study within an acceptable time frame; 4) Termination due to regulatory or ethical requirements.
Study Drugs	**Investigational Drug Group** GST-HG171 Strength: 150 mg Dosage and administration: 150 mg/time, orally, BID, for 5 consecutive days Shelf life: 12 months tentatively Manufacturer: Fujian Cosunter Pharmaceutical Co., Ltd. Supplier: Fujian Akeylink Biotechnology Co., Ltd. Ritonavir Strength: 100 mg Dosage and administration: 100 mg/time, orally, BID, for 5 consecutive days Shelf life: 24 months Manufacturer: Jiangsu Sinotherapeutics Co., Ltd. Supplier: Fujian Akeylink Biotechnology Co., Ltd. **Placebo Group** Placebo for GST-HG171 Strength: 150 mg Dosage and administration: 150 mg/time, orally, BID, for 5 consecutive days Shelf life: 12 months tentatively Manufacturer: Fujian Cosunter Pharmaceutical Co., Ltd. Supplier: Fujian Akeylink Biotechnology Co., Ltd. Ritonavir blank tablet

	Strength: 100 mg Dosage and administration: 100 mg/time, orally, BID, for 5 consecutive days Shelf life: 24 months tentatively Manufacturer: Ascletis Pharmaceuticals Co., Ltd. Supplier: Fujian Akeylink Biotechnology Co., Ltd.
Concomitant Medications and Therapies	**Prohibited Therapies** ● Subjects are prohibited from antiviral therapies against SARS-CoV-2 (e.g., Paxlovid, Molnupiravir, Azvudine, Simnotrelvir Tablets/Ritonavir Tablets, Deuremidevir Hydrobromide Tablets, etc.) within 14 days prior to randomization through Day 28 of the study; ● Subjects are prohibited from COVID-19 monoclonal antibody, intravenous injection of COVID-19 human immunoglobulin, or COVID-19 convalescent plasma therapy within 30 days prior to randomization or within 5 drug half-lives (whichever is longer) until D28 of the study; ● Subjects are prohibited from medications for the alleviation of COVID-19 symptoms from randomization to Day 28 of the study: antipyretics/analgesics, antitussives/expectorants, combination cold remedies, antihistamines**, antibacterials and antifungals (except for complications of suspected bacterial or fungal infection after Day 1 treatment), glucocorticoids**, immunosuppressants, Chinese herbal/patent medicines that have an adjunctive mitigating effect on COVID-19 symptoms, except for medications permitted in the *Medication Guide for Symptom Alleviation During the Study* (see Appendix 8). *Note: **The use of skin preparations is allowed, but they should not be used in the eyes, nose or ears or by inhalation.* ● Subjects are prohibited from receiving traditional Chinese medicine (e.g., acupuncture) or traditional Chinese medicine physiotherapy (e.g., cupping) to relieve COVID-19 symptoms from randomization to Day 28 of the study. ● Subjects are prohibited from using other investigational drugs within 3 months prior to administration through Day 28 of the study. ● Subjects are prohibited from use of drugs prohibited by the package insert of Paxlovid or any other drugs or substances (Appendix 4) that are highly dependent on CYP3A4, CYP2B6, CYP1A2, MDR1 or OATP 1B3 for clearance during study drug administration and within 4 days after the last dose. ● Subjects are prohibited from concomitant medications of any potent CYP3A4 or MDR1 of within 28 days prior to randomization and during the treatment of study drug until 4 days after the last dose (Appendix 4). *Note: For drugs not listed in Appendix 4, co-administration should not be assumed as safe. Investigators will review all concomitant medications prior to the first dose to determine if they are potent CYP3A4 or MDR1 inducers or are highly dependent on CYP3A4, CYP2B6, CYP1A2, MDR1, or OATP1B3 for clearance, which will be prohibited.* **Permitted Therapies** In addition to study interventions and prohibited medications, if subjects progress to severe/critical COVID-19 during the study, they are allowed to be treated in accordance with local guidelines for severe/critical COVID-19, with the exception of drugs prohibited by the package insert of Paxlovid or other drugs or substances highly dependent on CYP3A4, CYP2B6, CYP1A2, MDR1, or OATP1B3 for clearance

	within 4 days after the last dose of study drug. Symptomatic treatment Recovery of COVID-19-related symptoms is the primary endpoint of this study. If the relevant symptoms in the subject are mild, no intervention is required unless necessary, and it is recommended to observe the symptoms for 1-2 days first; if the subject remains intolerable and strongly requests medication, drug intervention can be considered as described in Appendix 8, but should be avoided whenever possible. If any medication for symptomatic treatment is used, the dosage, date and time of each dose should be recorded. Measurement of body temperature and assessment of COVID-19 symptoms will be performed before or more than 4 hours after symptomatic treatment.
Study Procedures	This study consists of three periods: screening period, treatment period, and post-treatment assessment period. Screening period Subjects can enter the treatment period after completing all the tests in the screening period, obtaining the test results, and being judged by the investigator to meet the eligibility criteria. Treatment period Eligible subjects are randomly assigned to the investigational drug group or the placebo group in a 1:1 ratio, with subjects in the investigational drug group receiving GST-HG171 plus ritonavir, and subjects in the placebo group receiving placebo for GST-HG171 plus ritonavir blank tablet, and the study treatment will last for 5 days or until withdrawal. Post-treatment assessment period After subjects completing 5 days of treatment, efficacy and safety assessments will be performed according to the visit schedule specified in the Schedule of Activities until 28 days after the first study treatment. Any AE that occurs during the study will be followed up until the AE resolves or stabilizes or the subject is lost to follow-up.
Efficacy Endpoints	**Primary Efficacy Endpoint** 1. Time to sustained recovery of clinical symptoms within 28 days after treatment. *Note: Sustained recovery of clinical symptoms is defined as with the score of 0 for all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) (see Appendix 1) for 2 consecutive days. Time to sustained recovery of clinical symptoms is defined as the number of days from the first dose after randomization to the first day when all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) are scored 0 for 2 consecutive days.* **Key Secondary Efficacy Endpoint** 1. Changes in viral load from baseline on Day 4 after treatment. 2. Time to sustained recovery of fever and respiratory symptoms within 28 days after treatment. *Note: the sustained recovery of fever and respiratory symptoms means that the scores (see Appendix 1) of fever and respiratory symptoms (cough, congestion or*

	runny nose, sore throat or dry throat, shortness of breath or difficulty breathing) are 0 for 2 consecutive days. Time to sustained recovery of fever and respiratory symptoms is defined as the number of days from the first dose after randomization to the first day when fever and respiratory symptoms (cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing) are scored 0 for 2 consecutive days. 3. Time to negative conversion of SARS-CoV-2 nucleic acid within 28 days after treatment. **Secondary Efficacy Endpoints** 1. Time to sustained alleviation of clinical symptoms within 28 days after treatment. *Note: Sustained alleviation of clinical symptoms is defined as with the score of ≤ 1 for all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) for 2 consecutive days. Time to sustained alleviation of clinical symptoms is defined as the number of days from the first dose after randomization to the first day when all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) are scored ≤ 1 for 2 consecutive days.* 2. Area under the viral load-time curve (AUC) within 14 days after treatment. 3. Clinical symptom score-time AUC within 14 days after treatment. 4. Percentage of subjects with COVID-19 progression (defined as progression to severe/critical COVID-19 or all-cause mortality) within 28 days after treatment. 5. Percentage of subjects with sustained recovery of clinical symptoms from baseline to each visit after treatment. 6. Changes in the scores of all COVID-19 symptoms from baseline to each visit after treatment. 7. Changes in the World Health Organization (WHO) Clinical Progress Scale (see Appendix 2) scores from baseline to each visit after treatment. 8. Changes in chest CT scan from baseline to Day 7 after treatment.
Safety Endpoints	The following will be assessed for clinical safety during the study: 1. Incidences of all AEs and serious adverse events (SAEs); 2. Any clinically significant abnormality of vital signs and physical examination; 3. Any clinically significant abnormality of laboratory tests and electrocardiograms during the study.
Pharmacokinetic (PK) Endpoints	1. Blood concentration and PopPK parameters of GST-HG171. 2. To explore the correlation of exposure/efficacy and exposure/safety for GST-HG171.
Statistical Analysis	**Sample Size** It is assumed that the median time to sustained recovery of clinical symptoms is 8 days for GST-HG171 and 10 days for placebo, then 960 subjects (480 in each group) need to be enrolled in a 1:1 ratio to achieve a power of 90% under the significance criterion with the one-sided of 0.0238 (two interim analyses require partial alpha spent), with 856 subjects expected to achieve sustained clinical symptom recovery. Accounting for a drop-out rate of about 20%, 1200 subjects are temporarily planned to be enrolled in this Phase II/III study, with 600 each in the investigational drug group

	and the placebo group. **Analysis Node** Two interim analyses, and a final analysis are planned to be performed for this study. The sentinel cohort safety review and preliminary efficacy observation (first interim analysis) are planned to be performed to review the sentinel cohort data and make a summary in an unblinded mode after approximately the first 100 sentinel cohort subjects have completed study drug treatment, received drug administration, and completed the D10 study visit assessments. The second interim analysis will be performed when about 60% of the subjects complete the D28 assessment. The final analysis will be performed after the last subject has completed the last assessment. The final analysis node may be adjusted according to the project condition. The boundary value generated by the Lan-DeMets spending function method to approximate O'Brien-Fleming will be used to control class I errors ($\alpha < 0.05$ for a two-sided test). **Analysis Sets** Full Analysis Set (FAS): All randomized subjects who have received at least 1 dose. Subjects will be analyzed according to their randomized groups. Modified Intent-to-Treat Analysis Set (mITT): Subjects in the FAS who are confirmed to be positive for SARS-CoV-2 nucleic acid by RT-PCR Fleming will be used to control class I errors (α at baseline and non-positive for influenza virus and have at least 1 visit from post-baseline to Day 28. Subjects will be analyzed according to their randomized groups. *Note: Baseline SARS-CoV-2 nucleic acid test is defined as the test result before D1 treatment; if there was no sampling on D1, the test result obtained at the time that is the closest to D1 during the screening period would be used as the baseline.* Per-Protocol Analysis Set (PPS): Subjects in mITT with those have major protocol deviations that may affect the primary efficacy analysis excluded. Protocol deviations will be reviewed at the blinded review meeting and a list of PPS subjects will be generated. The PPS will be determined prior to unblinding. Safety Analysis Set (SS): All subjects who have received at least 1 dose. Subjects will be analyzed according to the actual treatment received. Pharmacokinetic Analysis Set (PKS): All enrolled subjects who have received at least 1 dose of study drug, have at least 1 evaluable concentration after administration at the planned PK time point, and have no major protocol violation that may significantly affect PK assessments. **Efficacy Analysis** All statistical tests are subjected to two-sided tests. $P \leq 0.05$ indicates a statistically significant difference (unless otherwise specified). Quantitative variables will be described by mean, standard deviation, median, minimum, maximum, 1st quartile (Q1), and 3rd quartile (Q3). Categorical variables will be presented with number of cases and percentages by category. The comparison of the general profiles between the two groups will be analyzed using appropriate methods according to the types of variables. The group t test or Wilcoxon rank sum test will be used for the comparison of quantitative variables between groups, the chi-square test or exact probability method will be used for categorical variables, the Wilcoxon rank sum test or CMH test will be used for rank variables, and the log-rank test will be used for time to event variables. Efficacy data will also be tabulated in detail.

Primary estimand

Target population: patients with positive SARS-CoV-2 RT-PCR test results and non-positive influenza virus test results, accompanied by at least two COVID-19 target symptoms (COVID-19 target symptoms include fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, and vomiting), including at least one designated symptom (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing), other requirements are listed in inclusion and exclusion criteria.

Treatment: Oral administration of GST-HG171 plus ritonavir or placebo for GST-HG171 plus ritonavir blank tablet as required by the protocol for 5 consecutive days.

Primary efficacy endpoint: Time to sustained recovery of clinical symptoms within 28 days after treatment. Sustained recovery of clinical symptoms is defined as with the score of 0 for all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) for 2 consecutive days. Time to sustained recovery of clinical symptoms is defined as the number of days from the first dose after randomization to the first day when all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) are scored 0 for 2 consecutive days.

Intercurrent events and handling strategies:

Intercurrent event name	**Handling strategy**
Use of prohibited medications or therapies that affect the efficacy endpoints* (see definition in Section 6.1.2)	Adopt combination strategy: for use of prohibited medications or therapies before recovery, treat as unrecovered an censor at 28 days
Use of concomitant drugs other than prohibited medications or therapies that affect the efficacy endpoints*	Use of therapy strategy
Early withdrawal from treatment: (1) Early discontinuation of treatment due to AE (2) Poor medication compliance (< 80%)	Use of therapy strategy
Early withdrawal from treatment: (1) Progressed to severe/critical COVID-19 (2) The efficacy is poor as assessed by investigators	Adopt combination strategy: patients wh progressed to severe/critical COVID-19 before recovery or were assessed by investigators as having poor efficacy an were withdrawn from treatment early were treated unrecovered and censored a 28 days
Delayed or interrupted administration due to AE	Use of therapy strategy
Death	Adopt combination strategy: for death before recovery, treat as unrecovered an censor at 28 days

*Prohibited medications or therapies that affect the efficacy endpoints will be

	identified at the data review meeting. Population level summary: Kaplan-Meier method will be adopted to calculate the median time to sustained recovery of clinical symptoms, time to 25% recovery, and time to 75% recovery as well as the corresponding two-sided 95% confidence intervals at the time of three sites in two groups, and Kaplan-Meier curves are drawn. Compare the time to sustained recovery of clinical symptoms between the two groups of subjects using the log-rank test adjusted for randomization factors. Cox regression model will be adopted to calculate the hazard ratio (HR, investigational drug group/control group) of sustained recovery of clinical symptoms corrected by randomization factors and its two-sided 95% confidence interval by taking study grouping and randomization factors as independent variables and condition of and time to sustained recovery of clinical symptoms of subjects as dependent variables. In order to assess the robustness of the primary analysis results, the following sensitivity analysis is initially planned, which will be further refined in SAP subsequently: ● Compare the time to sustained recovery of clinical symptoms between the two groups of subjects using the uncorrected log-rank. ● Cox regression model will be adopted to calculate the hazard ratio (HR, investigational drug group/control group) of sustained recovery of clinical symptoms and its two-sided 95% confidence interval by taking study grouping as independent variables and condition of sustained recovery of clinical symptoms and time to sustained recovery of clinical symptoms of subjects as dependent variables. ● For the concomitant events "Use of prohibited medications or therapies that affect the efficacy endpoints", "withdrawing from treatment early due to progression to severe/critical COVID-19", "poor efficacy as assessed by the investigator" and "death", patients will be censored on the same day when the concomitant events occurred. ● For the missing values without concomitant events, censoring is at 28 days. ● In addition to sensitivity analysis, this study also preliminarily plans to do the following supplementary analysis, which will be further improved in SAP: ● Adopt different management strategies (“therapy strategies”) for concomitant events "Use of prohibited medications or therapies that affect the efficacy endpoints", "withdrawing from treatment early due to progression to severe/critical COVID-19", "poor efficacy as assessed by the investigator" and "death". ● Perform the same analysis as the primary analysis based on the FAS analysis set. ● Perform the same analysis as the primary analysis based on the PPS analysis set. ● Considering the actual possible imbalance of other covariates and thinking that they may potentially affect the evaluation of the treatment effect, in the stratified COX regression model of the primary analysis, other covariates considered as necessary by the project team will be included. **Safety Analysis** AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (the latest version will be used for statistical analyses), and descriptive statistical analysis will be conducted by System Organ Class (SOC)/Preferred Term (PT). The incidences of AEs, treatment-emergent adverse events (TEAEs), study drug-related AEs, and SAEs will be calculated overall and by SOC/PT. The incidences and number

	of TEAEs and study drug-related AEs will be summarized by SOC and severity. AEs, TEAEs, study drug-related AEs, SAEs, etc. will be tabulated in detail. For laboratory tests, shift tables will be generated to display normal/abnormal changes before and after administration. Laboratory test results will be tabulated in detail. For ECGs, shift tables will be generated to display normal/abnormal changes before and after administration. ECG results will be tabulated in detail. The results of each variable of vital signs and physical examination at each visit will be presented using descriptive statistics and tabulated in detail. See General Principles for analytical methods. **PK Analysis** Based on the obtained blood concentration data, a PopPK model of GST-HG171 will be constructed using a nonlinear mixed effect model, and the effect of internal/external factors on the PK characteristics of GST-HG171 will be assessed. If the data permits, the individual exposure parameters of patients will be estimated based on the parameter estimates of the established final PK model for further dose-response (exposure-response) analysis, including an exploratory analysis of the correlation of exposure/efficacy and exposure/safety. The specific analysis method of PopPK above is shown in the separate PopPK analysis plan, and the analysis results will be provided in a separate report separated from the clinical summary report. **Interim Analyses** The sentinel cohort safety review and preliminary efficacy observation (first interim analysis) are planned to be performed to review the sentinel cohort data and make a summary in an unblinded mode after approximately the first 100 sentinel cohort subjects have completed study drug treatment, received drug administration, and completed the D10 study visit assessments. Enrollment of subjects will be continued during the DSMB review of sentinel cohort data, but the study may be suspended or terminated as recommended by the DSMB. The second interim analysis will be performed when about 60% of the subjects complete the D28 assessment. In this interim analysis, unblinded sample size re-estimation/futility analysis will be conducted. Based on the conditional power, if the interim analysis results fall in the expected interval (conditional power between 50% and 80%), the sample size will be increased by 480 at most, resulting in the total sample size in the primary analysis set mITT to approximately 1440 cases. The Cui, Hung, and Wang's weighted test statistic will be used to control the Type I error rate as the sample size increases. The specifics of sample size re-estimation will be provided in the interim analysis plan, and an unblinded team will be established to draft the interim analysis plan and complete the interim analysis tasks. The interim analysis will support DSMB to provide recommendations for the implementation of the study: ● In case of significant safety issues, the DSMB recommends the sponsor to terminate the trial. ● If the termination criteria due to ineffectiveness are met according to the analysis results, the trial can be terminated. The conditional power for estimating the proposed termination criteria due to ineffectiveness based on the analysis results is < 5%. ● If the conditional power for estimation based on the analysis results is between 50% and 80%, it is recommended to continue the study on the basis of increasing

the number of target events, and conduct the final analysis when the updated number of target events is reached (the significance criterion is two-sided 0.0476).

- Otherwise continue the trial with the original planned sample size.
- Type I error spending calculated by SAS software for sentinel cohort data review (first interim analysis), second interim analysis, and final analysis is shown in the table below.

Analysis	Information proportion	Two-sided Type I error spending
Sentinel cohort data review (first interim analysis)	10%	<0.00001
Second Interim Analysis	60%	0.00762
Final Analysis	100%	0.0476

*The information proportion in the sentinel cohort data review (the first interim analysis) is the proportion of the primary analysis population accounting for 960 subjects; the information proportion of the second interim analysis is the proportion of the primary analysis population accounting for 960 subjects with sample size adjustment.

**In case that the actual cumulative proportion of information is inconsistent with the original plan, the type I error spending will be calculated based on the actual proportion of information.

Subgroup Analysis

In this study, gender, age (≤ 65 years vs. 65-75 years vs. > 75 years), mild vs. moderate, and COVID-19 vaccination or not are considered initially for subgroup analysis, which will be further refined in SAP.

Detailed statistical analysis methods will be elaborated in the SAP.

SCHEDULE OF ACTIVITIES

Visit	Screening period[x]	Treatment period					Post-treatment assessment period[y]					
	D-5 ~ D1	D1	D2[y]	D3[y]	D4	D5[y]	D7	D10	D14	D21	D28 （EOS）	Early withdrawal
Time window	/	/	/	/	/	/	/	±1	±2	±2	+3	+7
Number of visits	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	
Informed consent	X											
Assignment of screening number	X											
Verification of inclusion/exclusion criteria	X	X										
Demographics[a]	X											
Height/weight[b]	X											
Past medical history[c]	X											
Surgery history	X											
Prior/concomitant medications[d]	X											
COVID-19 risk factor assessment[e]	X											
Physical examination[f]	X	X			X		X*	X*	X*	X*	X*	X*
Vital signs and oxygen support[g]	X	X			X		X*	X*	X*	X*	X*	X*
12-lead ECG[h]	X	X			X		X*		X*		X*	X*
Pathogenic test[i]	X											
Urine pregnancy[j] (for WOCBP only)	X										X*	X*
Laboratory tests (including hematology, serum biochemistry, urinalysis and CRP)[k]	X	X[k]			X				X*		X*	X*
SARS-CoV-2 IgM/IgG[l]	X[l]	X[l]										
CD3/CD4/CD8, procalcitonin, erythrocyte sedimentation rate and IL-6[m]		X			X				X*		X*	X*
Qualitative test of SARS-CoV-2 nucleic acid[n]	X	X			X		X*	X*	X*	X*	X*	X*
Quantitative test of SARS-CoV-2	X	X			X		X*	X*	X*	X[o]	X*	X*

Visit	Screening period[x]	Treatment period					Post-treatment assessment period[y]					
	D-5 ~ D1	D1	D2[y]	D3[y]	D4	D5[y]	D7	D10	D14	D21	D28 （EOS）	Early withdrawal
Time window	/	/	/	/	/	/	/	±1	±2	±2	+3	+7
Number of visits	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	
nucleic acid[o]												
Determination of SARS-CoV-2 virus strain[p]		X										
Influenza virus detection	X											
Chest CT[q]	X	X[q]					X [q]*					
PopPK sampling[r]		X			X							
Randomization	X											
Administration[s]		X	X	X	X	X						
Assessment of COVID-19-related Symptom Score Scale[t]	X											
Assessment of WHO Clinical Progression Scale[u]	X	X	X	X	X	X	X	X	X	X	X	X
Subject Diary Card[v]		X[v]										
Collection of AEs[w]	X											
Recording of concomitant medications and therapies	X											

Abbreviations: COVID-19 = Corona Virus Disease 2019; WOCBP = women of childbearing potential; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; IgM = immunoglobulin M; IgG = immunoglobulin G; CRP = C-reaction protein; IL-6 = interleukin-6; CT = computerized tomography; PopPK = population pharmacokinetics; WHO = World Health Organization

Note:

a) Demographics include gender, ethnicity, and date of birth.

b) Height, weight and body mass index (BMI). Height is measured in m and weight in kg, with shoes removed and light clothing worn.

c) Past medical history includes disease history, allergy history, dates of diagnosis of COVID-19 and onset of symptoms of COVID-19, and time of COVID-19 vaccine or prophylactic antibody vaccination, and is recorded by way of doctor's interview.

d) Prior medications include the time and name of previous treatments of special interest for COVID-19.

e) High risk factors for progression to severe COVID-19: elderly people aged > 65 years old, especially those who have not received full-course vaccination against COVID-19; patients with underlying diseases such as cardiovascular disease (including hypertension), chronic lung disease, diabetes mellitus, chronic liver and

kidney disease, and tumors and patients on maintenance dialysis; patients with immune deficiency (e.g., AIDS patients, long-term use of corticosteroids or other immunosuppressants leading to a decreased immune function); patients with obesity (BMI ≥ 30); heavy smokers.

f) Physical examination: A thorough physical examination is conducted during the screening period and simple physical examination is conducted as indicated by the subject's status and standard of care during the study.

g) Vital signs and oxygen support: Including temperature, pulse rate, blood pressure, respiratory rate, SpO_2 and inspired oxygen flow (if applicable), fraction of inspired oxygen (FiO_2) (if applicable), mode of oxygen delivery (if applicable), and oxygen support procedures (if applicable). The investigator can adjust the specific test items according to the patient's condition. The blood pressure and pulse should be measured after the subject has rested for at least 5 minutes.

h) Electrocardiogram (ECG) is performed at the site visit only for the first 100 subjects (sentinel cohort) as indicated in the flow chart. ECG may be continued for subjects enrolled after the sentinel cohort as recommended by the DSMB. ECG should be performed after the first dose on D1, and the recommended time window is 0.5-1.5 h after administration. ECG at subsequent visits can be conducted according to the willingness of the subject and as assessed by the investigator without specific requirements. Based on the results of the second interim analysis, a determination can be made as to whether the subsequent subjects enrolled need to continue the ECG. All planned ECG examinations should be performed after the subject has rested for at least 5 minutes.

i) Pathogenic tests include: human immunodeficiency virus (HIV) antibody, Treponema pallidum-specific antibody (TP-PA), syphilitic rapid plasma reagin (RPR) positive for syphilis. Specific test items can be selected or adjusted according to the testing capability of the study site.

j) Urine pregnancy tests will be performed for women of childbearing potential during the screening period and at the last visit. During the study period, the serum pregnancy test may be added at the investigator’s discretion.

k) Laboratory tests: If laboratory tests have been performed within 72 hours before the first administration, they may not be repeated on D1.

l) There is no need for more SARS-CoV-2 IgM/IgG test after it is positive. If the test on D1 is negative, the investigator can decide whether to continue the test according to the patient's condition. Specific test items can be selected or adjusted according to the testing capability of the study site.

m) Specific test items can be selected or adjusted according to the testing capability of the study site.

n) Nasopharyngeal/oropharyngeal swab testing is acceptable during the screening period (results within 5 days prior to randomization are acceptable, a Ct value of < 35 of the RT-PCR result of N gene or ORF gene of SARS-CoV-2 must be required within 48 h prior to randomization), and nasopharyngeal swabs are collected at follow-up visits. If the subject is confirmed to be negative or progresses to severe/critical COVID-19, no sampling is required. Confirmed negative conversion is defined as two consecutive negative SARS-CoV-2 nucleic acid tests (at least 24 hours apart). If the negative conversion is not confirmed by nucleic acid test, it is recommended to continue sampling. If the subject is unable to return to the hospital for follow-up, a telemedicine visit can be conducted on D7 or later, and the formal qualitative nucleic acid result with Ct value in an external hospital is acceptable.

o) Nasopharyngeal swabs will be collected. Baseline SARS-CoV-2 nucleic acid test is defined as the test result before first dose on D1; if there was no sampling on D1, the test result obtained at the time that is the closest to D1 during the screening period would be used as the baseline. D21: It is recommended to continue sampling regardless of symptom recovery or confirmed negative conversion of nucleic acid test. Sampling is not required if it is a telemedicine visit.

p) SARS-CoV-2 variant typing is performed on the SARS-CoV-2 nucleic acid quantitative test samples for at least 10% of subjects.

q) D1: Assessments before administration are considered as baseline values. If chest CT examination is performed within 5 days before the first administration, it may not be repeated on D1. For subjects with baseline imaging findings of pneumonia, reassessment is performed on D7 as a secondary efficacy endpoint; for

subjects without baseline imaging findings of pneumonia, reassessment is not required on D7. Changes on D7 relative to baseline, including no change, deterioration, and improvement should be assessed by the investigator.

r) PK blood samples may be collected based on the subject's willingness. The collection time points include: within 2 hours before the first dose on D1, 0.5-1.5 hours after the first dose on D1, and within 2 hours before the first dose on D4. Sampling can be performed as appropriate for the actual situation. It is encouraged to at least collect the blood sample within 2 hours before the first dose on D4. If the PK blood sample is not collected, it may not be regarded as a protocol deviation.

s) If the administration starts on the morning of D1, it will end on D5; if the administration starts on the evening of D1, it will end on the morning of D6.

t) The subjects are required to fill in the COVID-19 related Symptom Scoring Scale every day, including 11 target symptoms and other COVID-19 symptoms (COVID-19 target symptoms including fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting). At least 2 COVID-19 target symptoms occur within 72 hours prior to randomization, including 1 designated symptom: fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath, or difficulty breathing. The symptom scoring on D1 should be completed prior to the first dose, and the COVID-19-related Symptom Score Scale should be completed at approximately the same time each day thereafter. The subject should score according to the worst severity of each symptom in the past 24 hours. Subjects may fill in the score scale under the guidance or assistance of the investigator. If it is a telemedicine visit, the investigator is to instruct the subject to complete it via telephone.

u) The investigator should complete the WHO Clinical Progression Scale after inquiring the subject. The scale scoring on D1 should be completed by the investigator prior to the first dose, and the WHO Clinical Progress Scale should be completed at approximately the same time for each visit thereafter. The investigator should score according to the worst severity of the subject in the past 24 hours. In case of telemedicine visit, the investigator will call the subject every visit to inquire about the subject and complete the WHO Clinical Progression Scale in a timely manner.

v) Subject diary cards will be dispensed at the D1 visit and be collected at the last visit.

w) Clinical adverse events that occur from the signing of the ICF by the subject to pre-dose of the first dose are recorded in the electronic Case Report Form (eCRF) as medical history/concomitant diseases and are not recorded as AEs/SAEs unless one of the following conditions is met: injury/damage caused by any clinical laboratory test operation (AEs related to study operating procedures); AEs caused by drug discontinuation associated with the study protocol; AEs caused by a drug other than the investigational drug taken as part of the treatment regimen.

x) D1 is the day for the first dose. If the screening period and D1 are on the same natural day, there is no need for all tests and assessments to be repeated. If they are on different and consecutive days, only the followings need to be repeated before the first dose on D1: qualitative and quantitative SARS-CoV-2 nucleic acid test, assessment of COVID-19-related Symptom Score Scale, assessment of WHO Clinical Progression Scale. Physical examinations, vital signs, and oxygen support are recommended to be repeated prior to D1 dosing, but are not mandatory. ECG is performed after D1 dosing, as detailed in Note h.

y) The subjects have telemedicine visits on D2, D3 and D5, and do not need to return to the study site. During the post-treatment assessment period, if a subject is unable to return to the study site for an on-site visit, a telemedicine visit may be conducted. In the case of telemedicine visit, the subjects should complete the COVID-19-related Symptom Score Scale every day to record the concomitant medications and treatments and AEs. The investigator will inquire about the subjects' condition by telephone at each visit time and complete the WHO Clinical Progression Scale. Items marked with * will not be performed in the case of telemedicine visits.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ACE-2	Angiotensin Converting Enzyme 2
ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC_{last}	Area Under the Plasma Concentration-Time Curve from Zero to the Last Quantifiable Time Point
BCRP	Breast Cancer Resistance Protein
BID	Twice Daily
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
C_{max}	Maximum Plasma Concentration Observed
COVID-19	Corona Virus Disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-reactive Protein
CS	Abnormal with Clinical Significance
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DM	Data Manager
DSMB	Data and Safety Monitoring Board
EC_{50}	Median Effect Concentration
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FE	Food Effect
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IC_{50}	Half-maximal Inhibitory Concentration
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin-6
IWRS	Interactive Web Response System
MAD	Multiple-dose Studies
MDR1	Multi-drug Resistance Gene 1

Abbreviation	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mITT	Modified Intention-to-Treat Analysis Set
NCS	Abnormal with No Clinical Significance
NMPA	National Medical Products Administration
NOAEL	No Observed Adverse Effect Level
OATP	Organic Anion Transporting Polypeptide
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PopPK	Population Pharmacokinetics
PPS	Per Protocol Set
QA	Quality Assurance
RNA	Ribonucleic Acid
RPR	Rapid Plasma Reagin for Syphilis
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAD	Single-dose study
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SDV	Source Data Verification
SS	Safety Set
SOC	System Organ Class
TID	Three times a day
T_{max}	Time to Maximum Concentration
TP-PA	Treponema Pallidum Specific Antibody
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBil	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TG	Triglyceride
ULN	Upper Limit of Normal
URL	Uniform Resource Locator
VOC	Variants of Concern
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

1. Study Background

1.1 Disease Introduction

The Corona Virus Disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Since the outbreak at the end of 2019, COVID-19 is still a global pandemic. The World Health Organization (WHO) data showed that as of October 8, 2022, a total of 617,597,680 confirmed cases and 6,532,705 deaths have been reported in 224 countries or regions around the world[1].

SARS-CoV-2 belongs to the beta coronavirus family along with the severe acute respiratory syndrome coronaviruses (SARS-CoV) discovered in 2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) discovered in 2012. SARS-CoV-2 has an envelope, whose virus particles are spherical or oval in shape and 60-140 nm in diameter. It contains four structural proteins: nucleoprotein (N), viral envelope (E), matrix protein (M) and spike protein (S)[2].

Like other viruses, SARS-CoV-2 genome also has variations, some of which influence biological characteristics of the virus. For example, the change in the affinity of S protein with angiotensin converting enzyme 2 (ACE-2) will have an impact on the ability of virus to invade cells, replicate and transmit, the generation of antibodies in recovered patients during convalescence and after vaccination, and the neutralizing ability of antibody drugs, thereby attracting extensive attentions. WHO proposed five variants of concern (VOCs), that is, Alpha, Beta, Gamma, Delta, and Omicron. At present, the Omicron variant has replaced Delta as the dominant epidemic strain[2].

SARS-CoV-2 is highly contagious and spreads quickly, mainly invading the respiratory system, with viral pneumonia as the prominent manifestation, and can also invade various organs throughout the body and cause related symptoms, which can lead to death in severe cases. With the emergence of highly contagious variants such as Omicron, COVID-19 has spread more rapidly, causing a serious burden on national health and social economy.

1.2 Current Treatment Regimen

So far, many vaccines and drugs against SARS-CoV have been approved for marketing. According to the *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 10)*[2] of China, the clinical classification of COVID-19 includes mild, moderate, severe and critical. Different treatment regimens should be adopted for patients with different clinical classifications. The antiviral drugs recommended in the *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 10)* include Paxlovid, Azvudine Tablets, Molnupiravir Capsules, amubarvimab/romlusevimab injection, intravenous injection of COVID-19 human immunoglobulin, convalescent plasma collected from recovered patients, and other drugs against SARS-CoV-2 approved by the National Medicinal Products Administration (NMPA), etc. Immunotherapy and anticoagulant treatment can also be used for severe and critical patients. In the *Therapeutics and COVID-19* living guideline[3] updated by the WHO on

September 16, 2022, for non-severe patients, Paxlovid are strongly recommended; antiviral oral drugs molnupiravir and remdesivir are recommended conditionally. However, the monoclonal antibodies sotrovimab and REGN-COV2 (casirivimab-imdevimab) have poor *in vitro* neutralizing activity against the variants, so they were changed from strong recommendations, replacing the previous conditional recommendations for their use.

As mentioned above, the treatment with neutralizing antibody used in the early stage is getting increasingly ineffective with the constant variation of COVID-19, and intravenous injection is not convenient but expensive. At the same time, the SARS-CoV-2 variants have the characteristics of fast transmission, strong virulence and easy immune escape, which lead to the continuous changes in the disease characteristics of patients infected with the virus. Therefore, mild to moderate patients infected with the variants still have unsatisfied antiviral treatment needs. Effectiveness of oral small molecule drugs that act on viral ribonucleic acid (RNA) replication is not susceptible to variants, and have the advantages of low production cost and good patient compliance. Hence, they are expected to become a better choice for the treatment of COVID-19.

1.3 Development of GST-HG171

1.3.1 Background

3CL protease plays a key role in virus replication and is an important target for the development of small molecule drugs against COVID-19. After SARS-CoV-2 virus enters the host cell by infection, with the help of the host cell, its genetic material RNA first translates and expresses two polyprotein precursors (pp1a and pp1ab). The polyprotein precursors undergo intramolecular cleavage under the action of 3CL protease and PL protease to produce multiple non-structural proteins. Since 3CL protease is responsible for the cleavage of at least 11 sites, it is also called the main protease (Mpro). These non-structural proteins are involved in the production of viral sub gene RNA and four structural proteins, thus completing the reproduction and release of the progeny virus. Therefore, inhibiting the activity of 3CL protease can prevent virus replication and achieve the purpose of treating COVID-19[4]. 3CL protease is relatively conservative in coronaviruses, and the substrates of 3CL protease of different coronaviruses have common characteristics, which means that inhibition of 3CL protease can act on many coronaviruses, while maintaining high activity against COVID-19 variants. In addition, 3CL protease is not expressed in the host, so 3CL protease inhibitors have high safety. In addition, compared with other therapeutic methods such as neutralizing antibodies targeting spike proteins, small molecule 3CL protease inhibitors have incomparable advantages: (1) The target is highly conservative, and drug-resistant mutations are unlikely to occur; (2) The oral administration method is simple and the patient's compliance is strong; (3) The production capacity is less limited, and the cost is lower than that of macromolecular drugs such as neutralizing antibody; (4) The storage and transportation conditions are easy to meet and have strong popularity. Therefore, small molecule 3CL protease inhibitors have great application prospects.

At present, Pfizer's 3CL protease inhibitor nirmatrelvir has been approved by many countries for the treatment of patients with mild to moderate COVID-19. Recently, Shionogi also announced that its 3CL protease inhibitor ensitrelvir fumaric acid (S-217622) has reached the primary endpoint of the Phase 3 clinical study.

Pfizer's Paxlovid is composed of two active ingredients--one is the 3CL protease inhibitor nirmatrelvir, and the other is the cytochrome P450 (CYP) 3A4 inhibitor ritonavir. Ritonavir itself has no activity for 3CL protease, but can slow down the decomposition of nirmatrelvir to maintain its activity for a longer time. For non-hospitalized COVID-19 patients with mild to moderate symptoms and high risks, Paxlovid has significant efficacy: on Day 28 of the study, the number of COVID-19-related hospitalizations or deaths among patients receiving Paxlovid (3/389 [0.77%]; 0 death) was significantly smaller than the number in patients receiving placebo (27/385 [7.01%]; 7 deaths), and the relative risk was decreased by 89.1%. In the final analysis of patients who started treatment within 3 days after the onset of symptoms and did not receive monoclonal antibodies, by Day 28, 5 (0.72%) of 697 patients in the Paxlovid group and 44 (6.45%) of 682 patients in the placebo group were hospitalized due to COVID-19 or died due to any cause, and the relative risk was decreased by 88.9%. The evaluation of viral load data in 1,574 patients (70% of 2,246 patients) showed that if the treatment was started 3 or 5 days after the onset of symptoms, compared with placebo, treatment with Paxlovid significantly reduced the viral load on Day 5. In terms of safety, the incidence of adverse events (AEs) during or after treatment was similar between the Paxlovid group (22.6%) and the placebo group (23.9%). Among patients treated with Paxlovid, the most commonly reported events (affecting at least 1% of patients) were taste disorder (5.6% vs. 0.3%), diarrhoea (3.1% vs. 1.6%), increased fibrin D-dimer (1.9% vs. 2.8%), increased alanine aminotransferase (ALT) (1.5% vs. 2.4%), headache (1.4% vs. 1.3%), decreased renal creatinine clearance (1.4% vs. 1.6%), nausea (1.4% vs. 1.7%), and vomiting (1.1% vs. 0.8%). These AEs were all non-serious adverse events (non-SAEs). Patients receiving Paxlovid reported fewer Grade 3 or Grade 4 AEs than those receiving placebo (4.1% vs. 8.3%), fewer SAEs (1.6% vs. 6.6%), and fewer AEs leading to drug withdrawal or placebo treatment (2.1% vs. 4.2%)[5]. A recently published real-world study was carried out in Hong Kong where Omicron BA.2.2. variants were popular, and included 1,074,856 non-hospitalized COVID-19 patients. The results showed that compared with the control group without receiving drugs, the use of molnupiravir reduced the risk of death by 24%, and the risk of disease progression after hospitalization by 43%, but did not reduce the risk of hospitalization. However, the use of Paxlovid reduced the risk of death by 66%, the risk of hospitalization by 23%, and the risk of disease progression after hospitalization by 43%. As can be seen from the study results, the two small molecule antiviral drugs could still maintain good efficacy on Omicron BA.2.2. variants, and Paxlovid could bring greater clinical benefits to patients[6].

In Shionogi's Phase III study of ensitrelvir, ensitrelvir could significantly shorten the time to elimination of five typical Omicron-related symptoms in mild to moderate COVID-19 patients

compared with placebo (median time 167.9 h vs.192.2 h); on Day 4, the viral RNA level in the ensitrelvir group was decreased by more than 1.4 log_{10} copies/mL from baseline, and the decrease was significantly greater than that in the placebo group. In addition, ensitrelvir showed good safety and tolerability in the study, and no SAE or death was found in the study[7].

The results of these clinical studies prove that 3CL protease inhibitors have good efficacy and safety in patients with mild to moderate COVID-19.man immunodeficiency virus Based on the huge therapeutic potential of 3CL protease inhibitors, Fujian Akeylink Biotechnology Co., Ltd. has developed GST-HG171, a 3CL protease inhibitor, which is registered as an innovative drug, class 1 of chemical drug. The nonclinical data of GST-HG171 are superior or non-inferior to Pfizer's nirmatrelvir in terms of enzyme activity level, SARS-CoV-2 cell strain and SARS-CoV-2 Omicron variant, Delta test, pharmacokinetics (PK) data, and lung exposure. GST-HG171 is intended for the clinical treatment of adult mild/moderate COVID-19 patients.

1.3.2 Drug name and physiochemical properties

Drug name: GST-HG171

Chemical name: (1S, 3S, 4R)-N-((S)-1-cyano-2-((S)-2-oxopyrrolidine-3-yl)ethyl)-2-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butyryl)-2-azaspiro[bicyclic[2.2.1]heptan-5,1'-cyclopropane]-3-formamide

Molecular formula: C24H32F3N5O4

Molecular weight: 511.55

Strength: 150 mg

Dosage form: Tablet

Administration route: Oral administration

Description: Pink film-coated tablet, with white or off-white core

1.3.3 Non-clinical study

1.3.3.1 Pharmacological study

The *in vitro* antiviral activity study of GST-HG171 showed that GST-HG171 had a strong inhibitory activity against SARS-CoV-2 and coronavirus OC43, and the effect was better than that of Pfizer's compound nirmatrelvir. The anti-SARS-CoV-2 cell activity experiment showed that GST-HG171 had a strong inhibitory activity against SARS-CoV-2 and its variants, and its median effect concentration (EC_{50}) values were 0.079 μM for wild type (WT), 0.048 μM for Omicron, and 0.049 μM for Delta, respectively, showing a stronger virus-inhibitory activity than nirmatrelvir. GST-HG171 had no significant cytotoxicity, and had no inhibitory effect on four common respiratory viruses including influenza strain IFVA/PR/8/34 (H1N1) (EC_{50} > 100 μM), indicating its specificity against coronavirus.

The results of the *in vitro* enzymology test showed that GST-HG171 had a strong inhibitory

activity against SARS-CoV-2 Mpro wild type and P132H mutant type, and the half-maximal inhibitory concentration (IC_{50}) values were 1.8 nM and 3.5 nM respectively, slightly better than that of nirmatrelvir (~2 times). In a selectivity test, GST-HG171 did not have any inhibitory effect on five human homologous proteases including human cathepsin B (IC_{50} > 100 μM), indicating its excellent selectivity to SARS-CoV-2 Mpro (3CL) protease.

The results of the off-target effect study showed that GST-HG171 did not activate or inhibit 78 common safety-related targets (including GPCR, ion channels, enzymes, etc.), and its EC_{50} or IC_{50} values were greater than 10 μM. No off-target risk was found, indicating that GST-HG171 had high safety and specificity.

In the antiviral model of mice infected with coronavirus OC43, the dose-dependent protection of animals by GST-HG171, body weight growth rate and *in vivo* exposure were positively correlated with the dose, showing a good dose-response relationship. The effective dose of GST-HG171 monotherapy was 12.5 mg/kg, and the exposure at this dose was about 5235 nM/h. The efficacy of GST-HG171 was better than that of nirmatrelvir at the same dose of 25 mpk. In the H11-K18-hACE2 mouse model infected with SARS-CoV-2, GST-HG171 significantly reduced the lung viral load compared with the vehicle control; in addition, GST-HG171 at two doses (150 mg/kg and 450 mg/kg) was significantly superior to Pfizer's nirmatrelvir in inhibiting the lung viral load. At the same time, GST-HG171 could protect animals from weight loss caused by SARS-CoV-2 infection. The results of *in vivo* pharmacodynamic study showed that GST-HG171 could effectively inhibit the replication and infection of SARS-CoV-2 in mice, which provided important scientific evidence to support the clinical trials of GST-HG171.

Safety pharmacology study showed that the risk of GST-HG171 on cardiovascular system, central nervous system and respiratory system was very low.

1.3.3.2 PK study

GST-HG171 has shown low permeability in both Caco2 and MDCK-MDR1 cells. After intragastric administration to SD rats and Beagle dogs, GST-HG171 showed good druggability and oral bioavailability. GST-HG171 showed moderate plasma protein binding rates in plasma of mice, rats, Beagle dogs, cynomolgus monkeys and humans. As for metabolism, GST-HG171 was metabolized at a high rate in the liver cells of CD-1 mice, and at a moderate rate in liver cells of SD rats, Beagle dogs, cynomolgus monkeys and humans. The main metabolic pathway *in vitro* in liver microsomes and hepatocytes was monooxidation, and no human specific metabolite *in vitro* was found. After intravenous administration to SD rats, GST-HG171 exhibited a high clearance (the average clearance in male and female animals was 42.4 ml/min/kg), and moderate tissue volume of distribution (Vd_{ss}: 1.07 L/kg). After intragastric administration to rats, GST-HG171 was highly distributed in the lung tissue, and its lung exposure and lung/blood ratio were significantly higher than those of nirmatrelvir. After intravenous administration to Beagle dogs, GST-HG171 exhibited a low clearance (the average clearance in male and female Beagle dogs was 7.13 ml/min/kg), and moderate tissue volume

of distribution (Vd_{ss}: 0.491 L/kg).

In terms of drug-drug interaction, GST-HG171 had no significant inhibitory effect on the major human CYP subtypes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), and no time-dependent inhibitory effect. The phenotypic study of metabolic enzymes showed that CYP3A was the main metabolic enzyme of GST-HG171. GST-HG171 is probably the substrate of P-glycoprotein (P-gp) efflux transporter, rather than the substrate of breast cancer resistance protein (BCRP) transporter. GST-HG171 had a weak inhibitory effect on organic anion transport polypeptide (OATP) 1B3, and its IC_{50} value was 32.8 μM. It had no obvious inhibitory effect on P-gp, BCRP, OATP1B1, OAT1, OAT3, OCT2, MATE1 and MATE2-K.

1.3.3.3 Toxicological study

In the single-dose toxicological study, the maximum tolerated dose was 1000 mg/kg in rats, and 900 mg/kg in Beagle dogs.

In the 14-day repeat-dose test in SD rats, GST-HG171 was administered to SD rats by gavage at doses of 50, 200 and 600 mg/kg, once a day for 2 consecutive weeks, 14 times in total, with a recovery period of 2 weeks. Decreased total bilirubin (TBil) and triglyceride (TG) were observed at doses ≥ 50 mg/kg; slight vacuole formation of liver cells was seen under microscope at the dose ≥ 600 mg/kg. After a 2-week recovery period, the above indexes were found to be recovered. Therefore, under the test conditions, the no observed adverse effect level (NOAEL) in animals was 600 mg/kg. At this dose, the average maximum plasma concentration observed (C_{max}) and area under the plasma concentration-time curve from zero to the last quantifiable time point (AUC_{last}) of GST-HG171 in male animals on D14 were 24613.07 ng/mL and 126058.08 hr·ng/mL, respectively, and the average C_{max} and AUC_{last} in female animals on D14 were 26758.38 ng/mL and 211400.97 hr·ng/mL, respectively, which were 47 and 79 times the effective dose exposure [effective dose in mice: 12.5 mg/kg, corresponding exposure (2678 hr·ng/mL)].

In the 14-day repeat-dose test in Beagle dogs, GST-HG171 was administered to Beagle dogs by gavage at doses of 30, 100 and 300 mg/kg, once a day for 2 consecutive weeks, 15 times in total, with a recovery period of 2 weeks. The clinical observation of animals in ≥ 30 mg/kg dose group showed excessive saliva secretion, vomiting, soft stool, loose stool, jelly-like substances in feces, and green substances in feces. Microscopic observation showed slight swelling of liver cells around the portal area, and recovery was observed after drug withdrawal. At a dose of 300 mg/kg, a transient increase in heart rate related to the test article was observed. Therefore, the NOAEL under this test conditions was 300 mg/kg. At this dose, the average C_{max} and AUC_{last} in male animals after the last dose (D15) were 91287.85 ± 22287.35 ng/mL and 539.88 ± 144.20 hr·μg/mL, respectively, and the average C_{max} and AUC_{last} in female animals were 92564.15 ± 20380.11 ng/mL and 512.17 ± 122.23 hr·μg/mL, respectively, which were 202 and 191 times the effective exposure *in vivo*. There was a sufficient safety window to

support Phase 1 clinical study. The repeat-dose toxicity in the two species was relatively consistent, which was basically consistent with the drug toxicity of drugs under study with the same target.

In this experiment, no obvious toxicity was observed at the highest dose in the two species. At the same time, the exposure in the two species increased with the increase of dose, and no drug accumulation was found, indicating that the possible toxicity risks of GST-HG171 in clinical use can be well predicted and monitored.

The results of three tests in the standard genotoxicity testing battery (bacterial reverse mutation test, *in vitro* chromosome aberration test and mouse bone marrow micronucleus test) were all negative, suggesting that GST-HG171 had no carcinogenic risk.

No independent reproductive toxicity test has been carried out in this project, but in the repeat-toxicity test in rats and Beagle dogs, detailed histopathological examinations were carried out on the organs related to the reproductive system of rats and Beagle dogs, and no abnormal changes were found. The results showed that GST-HG171 had no obvious toxic effect on the reproductive system.

1.3.4 Clinical study

A phase 1 clinical study on the safety and tolerability of single and multiple consecutive administrations, drug interaction and food effects of GST-HG171 in Chinese adult healthy subjects has been completed.

Safety conclusion: A total of 78 subjects were enrolled, of which 32 were enrolled in the single ascending dose (SAD) study (150 mg, 300 mg, 600 mg, and 900 mg, respectively for the four dose groups), and 8 subjects were enrolled in each dose group, of which six received GST-HG171 tablets and two received placebo, both male and female. Eight subjects were enrolled in the drug interaction study (150 mg dose group), and 14 subjects were enrolled in the food effect (FE) study (8 of whom were also subjects in the SAD study) and randomized into two groups, with 6 of the 8 subjects in group A receiving the test drug and 2 receiving placebo, and all 6 subjects in group B receiving the test drug (300 mg). Thirty-two patients were enrolled in the multiple ascending dose (MAD) study (4 dose groups, 300 mg BID, 150 mg + Ritonavir BID, 300 mg 3 times a day [TID], and 300 mg + Ritonavir BID, respectively).

In all 78 subjects, the incidence of adverse events(AEs) in the investigational drug group was comparable to that in the placebo group, with no deaths, SAEs, no Grade III or higher drug-related AEs, and no clear dose-related incidence of investigational drug-related treatment-emergent adverse even(TEAE) with ascending dose was observed. Only 4 subjects in the trial experienced 5 CTCAE 5.0 grade II AEs (hyperuricaemia, hypertriglyceridemia, decreased white blood cell count, decreased neutrophil count and hypoglycaemia), and the remaining AEs were all grade I in severity. Common AEs possibly related to the investigational drug mainly included hypertriglyceridemia, elevated ALT, elevated aspartate aminotransferase (AST) and other laboratory abnormalities, bitter taste and transient gastrointestinal reactions. On the basis

of safety test results, no significant change trend was observed in hematology, blood biochemistry, vital signs or ECG in the subjects before and after administration. No TEAE leading to discontinuation or withdrawal occurred in any subject.

The subjects were safe and well tolerated in all dose groups for SAD study, drug interaction study, FE study and MAD study for GST-HG171 Tablets.

Pharmacokinetic conclusions:

SAD study: The pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of GST-HG171 single dose increased in the dose range of 150 mg to 900 mg, but the exposure of GST-HG171 in 900 mg group was saturated to a certain extent. The median time to maximum concentration (T_{max}) of GST-HG171 in plasma for each dose group ranged from 0.50 to 0.75 h, with a mean $t_{1/2}$ of 2.38~5.34 h.

Drug interaction study: After oral administration of 150 mg GST-HG171 alone or 150 mg GST-HG171 + 100 mg Ritonavir combination in healthy subjects, Ritonavir significantly increased the *in vivo* exposure of GST-HG171 (C_{max}, AUC) by about 3~6 folds and by approximately 24-fold 12 h after dose concentration was increased, with almost no effect on T_{max} and $t_{1/2}$.

FE study: The geometric mean ratios of the pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for GST-HG171 were 92.18%, 103.13%, and 102.85% under high-fat fed and fasted conditions, respectively. Food had little or no effect on GST-HG171 exposure *in vivo*.

After a single oral dose of 300 mg GST-HG171 under fasted conditions, the mean cumulative urinary and fecal excretion rates of prototype GST-HG171 over 96 h were 6.48% and 0.25%, respectively. The prototype GST-HG171 was excreted mainly via the urinary system.

MAD study: 150 mg and 300 mg GST-HG171 administered in combination with Ritonavir BID resulted in a C_{max} and AUC accumulation ratio close to 1.5, with slight accumulation. 300 mg GST-HG171 BID and TID administered alone resulted in a C_{max} and AUC accumulation ratio of less than 1, with essentially no accumulation. Steady state was generally achieved on the second day of administration. GST-HG171 exposure increased significantly when administrated in combination with Ritonavir compared to GST-HG171 alone and GST-HG171 exposure in plasma was significantly higher when 150 mg GST-HG171 was administered in combination with Ritonavir BID than 300 mg GST-HG171 BID and TID alone, especially at trough levels.

In summary, the results revealed that GST-HG171 was rapidly metabolized as a single agent, and the 150 mg GST-HG171 + 100 mg Ritonavir BID regimen is recommended. Multiple doses provided significantly higher exposure and more stable metabolism compared to a single dose, as well as safely tolerated dose, so the 150 mg GST-HG171 + 100 mg Ritonavir BID regimen is recommended as the phase II/III regimen.

1.4 Scientific Rationale for Study Design

According to the *Technical Guidelines for Clinical Trials of New Antiviral Drugs for COVID-*

19 (Trial), in confirmatory trials, the efficacy and safety of new drugs used to treat mild and/or moderate COVID-19, reduction of progression to severe/critical COVID-19 and deaths and promotion of clinical recovery are mainly evaluated in mild and/or moderate patients[8]. Accordingly, the primary objective of this study is to evaluate the efficacy and safety of GST-HG171 plus ritonavir in the treatment of mild/moderate COVID-19. The primary efficacy endpoint is set as the time to sustained recovery of clinical symptoms within 28 days after treatment. The primary endpoint will be assessed as of Day 28 of the study to allow sufficient time for a reliable assessment of the safety and efficacy of the 5-day regimen of GST-HG171 plus ritonavir.

According to the *Technical Guidelines for Clinical Trials of New Antiviral Drugs for COVID-19 (Trial)*, in the case that positive control drugs cannot be obtained, it is recommended to use a randomized, double-blind, placebo-controlled, superiority comparison add-on design based on the recognized background treatment[8]. At present, no comparable products have been fully approved in China. Even if other antiviral drugs have been approved with conditions or authorized for emergency use, no absolute efficacy of these drugs in the target population of this study has been observed. Therefore, there is no recognized positive control drug. Moreover, with the variation of virus strains and the change of prevention and control means, the recovery time of clinical symptoms for patients with mild/moderate COVID-19 has been quite different from the clinical study data of Paxlovid, a comparable drug. If it is used as a positive control drug, it is difficult to calculate the sample size based on the primary efficacy endpoint. Therefore, the design of this study follows the recommendations of the guidelines, and placebo for GST-HG171/ritonavir blank tablet is used as the control. Further, the main pathogenic strain currently prevalent worldwide is the Omicron variant, which is highly transmissible but less pathogenic, and most of the infected patients present with asymptomatic or mild infection and more obvious upper respiratory symptoms, with low severe rate[9]. Thus, the risk of setting placebo control in this study is low.

Subjects with positive SARS-CoV-2 test results for the first time within 5 days prior to randomization, a Ct value of < 35 of the RT-PCR result of N gene or ORF gene of SARS-CoV-2, at least 2 COVID-19 symptoms for the first time within 72 hours prior to randomization, and at least 1 designated symptom: fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath, or difficulty breathing were included in this study. Different studies have shown that the SARS-CoV-2 viral load is the highest in the early stage of the disease or 3-5 days after the onset, and then continues to decline[10]. In addition, with the progression of COVID-19 infection, host inflammation plays a dominant role in the later stage of the disease, so early antiviral treatment can bring greater benefits.

The rationale for dose selection for this study was as follows: the completed PK study revealed that 150 mg GST-HG171 administered in combination with Ritonavir twice a day resulted in a C_{max} and AUC accumulation ratio close to 1.5. 300 mg GST-HG171 BID administered alone resulted in a C_{max} and AUC accumulation ratio of less than 1. The GST-HG171 exposure

increased significantly when administrated in combination with Ritonavir compared with GST-HG171 alone, with more stable metabolism. The steady-state trough concentration was 790 ng/mL for 150 mg GST-HG171 combined with Ritonavir BID and 59.1 ng/mL for 300 mg GST-HG171 alone BID. Steady state was generally achieved on the second day of administration. GST-HG171 alone was metabolized rapidly, with a mean $t_{1/2}$ of 2.38-5.34 h and low trough concentration and GST-HG171 alone had a steady-state trough concentration of 59.1 ng/mL after 300 mg BID administration, which was difficult to cover the calculated EC_{50} value of novel coronavirus BA.5 *in vitro* (after plasma protein correction), approximately 131.87 ng/mL. Thus, with steady-state trough concentration of 790 ng/mL and provides good coverage of the EC_{50} approximately 6.0-fold, the dose regimen of 150 mg GST-HG171 + 100 mg Ritonavir BID is recommended. The steady-state trough concentration of Pfizer Paxlovid could cover its EC_{50} about 2.64 times. Besides, multiple doses of 150 mg GST-HG171 + 100 mg Ritonavir BID were safe and well-tolerated, therefore the 150 mg GST-HG171 + 100 mg Ritonavir BID dosing regimen is recommended as a phase II/III dosing regimen.

1.5 Risk-benefit Assessment

Completed nonclinical toxicological studies on GST-HG171 that can support this trial include a single-dose toxicological study, a repeat-dose toxicological study, a genetic toxicity test, and a preliminary assessment of drug interactions. The study results showed that GST-HG171 had good safety and tolerability.

At present, the pharmaceutical research and production of GST-HG171 are carried out in accordance with the relevant guidelines and regulations, and the quality is controllable. In addition, according to the obtained preclinical research results, it can be reasonably inferred that GST-HG171 will not cause any unknown or uncontrollable toxic reactions to humans.

The target of GST-HG171 is the same as that of Pfizer's nirmatrelvir, and a number of clinical studies on nirmatrelvir have been carried out around the world, suggesting that it is safe and well tolerated in humans. The safety analysis of the Phase 3 study of Paxlovid (nirmatrelvir combined with ritonavir) showed that the incidence of AEs during or after treatment was similar between the Paxlovid group (22.6%) and the placebo group (23.9%). Among patients treated with Paxlovid, the most commonly reported events (affecting at least 1% of patients) were taste disorder (5.6% vs. 0.3%), diarrohea (3.1% vs. 1.6%), increased fibrin D-dimer (1.9% vs. 2.8%), increased alanine aminotransferase (ALT) (1.5% vs. 2.4%), headache (1.4% vs. 1.3%), decreased renal creatinine clearance (1.4% vs. 1.6%), nausea (1.4% vs. 1.7%), and vomiting (1.1% vs. 0.8%). These AEs were all non-SAEs. Patients receiving Paxlovid reported fewer Grade 3 or Grade 4 AEs than those receiving placebo (4.1% vs. 8.3%), fewer SAEs (1.6% vs. 6.6%), and fewer AEs leading to drug withdrawal or placebo treatment (2.1% vs. 4.2%)[4].

At present, the COVID-19 epidemic has caused a serious burden on national health and social economy. The preclinical efficacy, PK and safety characteristics of GST-HG171, as well as the clinical research results of similar drugs, can support the clinical development of GST-HG171

as an anti-COVID-19 drug. Its successful development will further meet the urgent clinical needs of COVID-19 patients in China, have significant clinical significance, and bring economic and social benefits.

In order to control the risks in the study, the clinical trial protocol sets inclusion/exclusion criteria by referring to similar drugs and the results of preclinical safety studies. Subjects with low safety risks will be selected, and all subjects will be required to take fully effective contraceptive measures or non-heterosexual behaviors during the study drug treatment period and within 28 days after the end of study.

During the clinical trial, it is planned to closely monitor the subjects participating in the clinical trial in the following ways: recording vital signs, physical examination, and 12-lead electrocardiogram (12-ECG), conducting clinical laboratory tests (hematology, serum biochemistry, urinalysis, etc.), reporting AEs, and following up AEs according to the protocol. For the safety issues (including abnormal laboratory indexes) that arise, the investigator should give appropriate treatment to subjects according to the requirements of the trial protocol and clinical medical principles, so as to protect the interests of subjects.

Strict risk control measures have been formulated in the risk control plan to ensure the safety of subjects in the trial.

2. Study Objectives and Endpoints

Study Objectives	Study Endpoint
To evaluate the efficacy of GST-HG171 plus ritonavir compared to placebo in the treatment of mild/moderate COVID-19.	**Primary efficacy endpoint:** 1. Time to sustained recovery of clinical symptoms within 28 days after treatment. *Note: Sustained recovery of clinical symptoms is defined as with the score of 0 for all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) (see Appendix 1) for 2 consecutive days. Time to sustained recovery of clinical symptoms is defined as the number of days from the first dose after randomization to the first day when all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) are scored 0 for 2 consecutive days.* **Key secondary efficacy endpoint:** 1. Changes in viral load from baseline on Day 4 after treatment. 2. Time to sustained recovery of fever and respiratory symptoms within 28 days after treatment. *Note: the sustained recovery of fever and respiratory symptoms means that the scores (see Appendix 1) of fever and respiratory symptoms (cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing) are 0 for 2 consecutive days. Time to sustained recovery of fever and respiratory symptoms is defined as the number of days from the first dose after randomization to the first day when fever and respiratory symptoms (cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing) are scored 0 for 2 consecutive days.* 3. Time to negative conversion of SARS-CoV-2 nucleic acid within 28 days after treatment. **Secondary efficacy endpoints:** 1. Time to sustained alleviation of clinical symptoms within 28 days after treatment. *Note: Sustained alleviation of clinical symptoms is defined as with the score of ≤ 1 for all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) for 2 consecutive days. Time to sustained alleviation of clinical symptoms is defined as the number of days from the first dose after randomization to the first day when all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) are scored ≤ 1 for 2 consecutive days.*

	2. Area under the viral load-time curve (AUC) within 14 days after treatment. 3. Clinical symptom score-time AUC within 14 days after treatment. 4. Percentage of subjects with COVID-19 progression (defined as progression to severe/critical COVID-19 or all-cause mortality) within 28 days after treatment. 5. Percentage of subjects with sustained recovery of clinical symptoms from baseline to each visit after treatment. 6. Changes in the scores of all COVID-19 symptoms from baseline to each visit after treatment. 7. Changes in the WHO Clinical Progression Scale (see Appendix 2) scores from baseline to each visit after treatment. 8. Changes in chest CT scan from baseline to Day 7 after treatment.
To evaluate the safety of GST-HG171 plus ritonavir compared to placebo in the treatment of mild/moderate COVID-19.	1. Incidence rate of all AEs and SAEs; 2. Any clinically significant abnormality of vital signs and physical examination; 3. Any clinically significant abnormality of laboratory tests and electrocardiograms during the study.
To assess the population pharmacokinetic (PopPK) characteristics of GST-HG171 plus ritonavir in adult patients with mild/moderate COVID-19.	1. Blood concentration and PopPK parameters of GST-HG171. 2. To explore the correlation of exposure/efficacy and exposure/safety for GST-HG171.

3. Selection and Withdrawal of Subjects

3.1 Inclusion Criteria

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

1. Male or female subjects aged ≥ 18 years when signing the informed consent form (ICF);
2. Subjects with reverse transcription-polymerase chain reaction (RT-PCR) test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in specimens such as nasopharyngeal swabs/oropharyngeal swabs for the first time within 5 days prior to randomization, who meet the diagnostic and treatment criteria for mild and moderate cases in the *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 10)* issued by the National Health Commission of the People's Republic of China (see Appendix 7);
3. RT-PCR result of N gene or ORF gene of SARS-CoV-2 within 48 hours before randomization shows a Ct value of < 35; at least 2 COVID-19 target symptoms appeared for the first time within 72 hours before randomization (COVID-19 target symptoms include fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, and vomiting), including at least one designated symptom: fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing;
4. Women of childbearing potential (see Appendix 3 for the definition of "women of childbearing potential") must have a negative urine pregnancy test during the screening period. Subjects should take effective contraceptive measures throughout the study period since signing the informed consent form and within 28 days after the end of the study (see Appendix 3);
5. Subjects who are able to understand the study procedures and methods, and voluntarily participate in the study and sign the ICF after being fully informed.

3.2 Exclusion Criteria

Subjects meeting any of the following criteria will not be allowed to be included in this trial:

1. Subjects who are known to have hypersensitivity to any component of the investigational drug;
2. Subjects who meet diagnostic and treatment criteria for severe and critical cases in the *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 10)* issued by National Health Commission of the People's Republic of China (see Appendix 7);
3. Abnormal hepatic function at screening: total bilirubin ≥ 1.5 × upper limit of normal (ULN); ALT or AST ≥ 3 × ULN;
4. Human immunodeficiency virus (HIV) antibody positive, treponema pallidum-specific antibody (TP-PA) positive or rapid plasma reagin (RPR) positive for syphilis at screening;

5. Abnormal renal function at screening: serum creatinine ≥ 1.5 × ULN;
6. Subjects with impaired immune system (including those treated with corticosteroids* or other immunosuppressants*, or those with progression or recurrence of cancer) at screening;

*Note: *Patients using skin preparations are allowed to be enrolled, but the skin preparations cannot be used in the eyes, nose or ears or by inhalation.*

7. Acute onset of chronic respiratory diseases, including bronchial asthma and chronic obstructive pulmonary disease at screening;
8. There are suspected or confirmed acute systemic infections except for COVID-19 at the time of screening (for example, the pathogen detection indicates that it is complicated with influenza; there is a high possibility of bacterial infection as indicated by symptoms, signs, laboratory tests or imaging), which may interfere with the assessment of response to study intervention;
9. Any comorbidity requiring surgery within 14 days prior to randomization or during the study, or any life-threatening comorbidity within 30 days prior to randomization as determined by the investigator;
10. Subjects who are receiving HIV antiviral treatment at screening;
11. Treatment with SARS-CoV-2 antiviral drugs within 14 days prior to randomization;
12. Subjects who have received (within 30 days prior to randomization or within 5 drug half-lives, whichever is longer) or are expected to receive COVID-19 monoclonal antibody, intravenous injection of COVID-19 human immunoglobulin, or COVID-19 convalescent plasma therapy;
13. Subjects who have received any COVID-19 vaccine within 28 days prior to randomization or planned to receive any COVID-19 vaccine during the study;
14. Any drug prohibited by the package insert of Paxlovid that is currently used or expected to be used during treatment and within 4 days after the last dose of study drug, or any other drug or substance (Appendix 4) that is highly dependent on cytochrome P450 (CYP) 3A4, CYP2B6, CYP1A2, multidrug resistance gene 1 (MDR1) or organic anion transporting polypeptide (OATP) 1B3 for clearance; any potent CYP3A4 or MDR1 inducers used within 28 days prior to randomization or expected to be used during treatment and within 4 days after the last dose of study drug (Appendix 4);
15. Pregnant or lactating women;
16. Subjects who have participated in other clinical trials within 3 months prior to administration or are receiving other investigational drugs;
17. Subjects with other conditions that, in the judgment of the investigator, make them unsuitable for participation in this study.

3.3 Withdrawal from the Trial

3.3.1 Criteria for subject withdrawal

Subjects can withdraw from the study at any time during the study without giving any reason and will not be discriminated or revenged due to withdrawal from the study, without prejudice to their normal medical services. During the study, the withdrawal of subjects from treatment includes but is not limited to:

1. Subjects withdraw the ICF and voluntarily ask to withdraw from the study;
2. Subjects experience intolerable AEs, as judged by the investigator;
3. Subjects have poor compliance, which seriously affects the implementation of the clinical trial or the evaluation of clinical efficacy and/or safety, at the discretion of the investigator;
4. According to the investigator's judgment, the subject had poor efficacy;
5. The subject had progressed to severe/critical COVID-19;
6. Subjects stop receiving examinations or tests and are lost to follow-up (dropout) although they do not explicitly express their intention to withdraw from the study.

Except for the withdrawal of informed consent or loss to follow-up, the subjects who early withdraw from treatment are encouraged to stay in the study as much as possible, participate in the visit according to the time point specified in the Schedule of Activities, and allow to collect relevant data, but it was ultimately up to the subject to decide whether to withdraw from the study.

3.3.2 Handling of withdrawn subjects

The investigator must fill in the reason for the withdrawal from the trial/treatment of the subject in the electronic Case Report Form (eCRF), contact the subject who withdraws from the trial as far as possible, and complete an early withdrawal visit within 7 days after confirming the withdrawal of the subject as far as possible. Specific reasons for subject withdrawing consent from treatment or from the trial will be further documented. For subjects who withdraw from the study for any reasons, their eCRFs should be retained. If any subject withdrawn has an AE at the time of termination of the study, the follow-up requirements for the AE are shown in **Section 8.6**.

3.4 Premature Termination of the Study/Closure of the Study Site

The sponsor has the right to terminate this study at any time, and the sponsor and the investigator have the right to close the study site at any time. Of course, this condition can be implemented only after mutual negotiation. The termination of the study must be reported to the Ethics Committee and the Institutional Review Board. When the study is early terminated or the study site is closed early, all study materials (except the documents that must be kept at the site) must be returned to the sponsor. The investigator must keep other documents until notified of destruction by the sponsor. Reasons for the early termination of the study or the

closure of the study site include but are not limited to:

1. New information leads to an unfavorable risk-benefit profile of the investigational drug, for example:
    a. The investigational drug lacks efficacy, either in this study or in other studies;
    b. Significant previously unknown adverse reactions or known adverse reactions with unexpected high severity/incidence;
    c. Other adverse safety findings, including clinical examination and non-clinical manifestations.
2. The Sponsor considers that it is unreasonable to continue the aforesaid study due to medical, ethical or commercial reasons;
3. The difficulty in enrolling subjects makes it unlikely to complete the study within an acceptable time frame;
4. Termination due to regulatory or ethical requirements.

3.5 Definition of Study Completion

End of study is defined as the time when the last subject completes the study scheduled last visit.

4. Study Design

4.1 Study Type and Design Rationale

This is a multicenter, randomized, double-blind, placebo-controlled Phase II/III clinical study to evaluate the efficacy and safety of GST-HG171 plus ritonavir in the treatment of mild/moderate COVID-19 in adult patients.

In the study, 1200 adult patients with mild/moderate COVID-19 are planned to be enrolled (including patients who are at a high risk of progression to severe illness), and randomized into the investigational drug group or the placebo group in a 1:1 ratio (randomization stratification factors include presence of a high-risk factor of progression to severe illness, and COVID-19 vaccination status [incomplete basic immunization, completed basic immunization, completed booster immunization]). Subjects in the investigational drug group will be administered with GST-HG171 (150 mg/time, twice daily [BID]) plus ritonavir (100 mg/time, BID) and subjects in the placebo group will receive placebo for GST-HG171 plus ritonavir blank tablet for 5 consecutive days to assess the efficacy and safety of GST-HG171 plus ritonavir compared to placebo in the treatment of mild/moderate COVID-19 in adult patients.

An independent Data and Safety Monitoring Board (DSMB) will be established in this study to assess the efficacy and safety data of study treatment given to the subjects.

The study includes a sentinel cohort which consists of approximately the first 100 subjects. Unblinded safety data will be reviewed and preliminary efficacy (first interim analysis) will be observed by the DSMB when subjects in the sentinel cohort have completed investigational drug treatment and the visit assessment at Day 10 (D10). Enrollment of subjects will be continued during the DSMB review of sentinel cohort data, but the study may be suspended or terminated as recommended by the DSMB.

The second interim analysis is expected to be conducted by an independent statistician when about 60% of the subjects complete the D28 assessment, and the results of this analysis will be submitted to the DSMB for review to provide a recommendation on whether to adjust the sample size, terminate or proceed the study. The boundary value generated by the Lan-DeMets spending function method to approximate O'Brien-Fleming will be used to control class I errors ($\alpha < 0.05$ for a two-sided test).

The study duration for each subject is up to 33 days (including up to 5 days for screening period, and 28 days for treatment period and post-treatment assessment period). The schematic diagram of the study is shown as below:

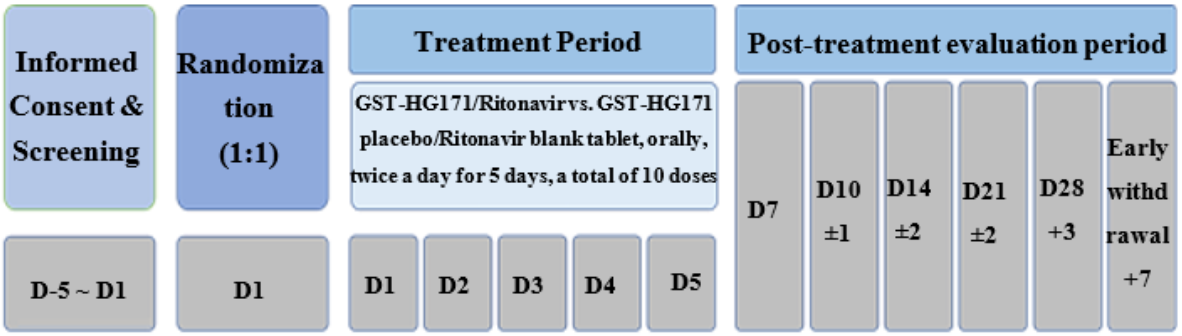

Figure 1 Schematic Diagram of Study Design

4.2 Randomization and Blinding

4.2.1 Randomization method

This study is designed as a randomized, double-blind, placebo-controlled study.

A randomization list will be generated by the randomization statistician using the PLAN procedure of SAS version 9.4 or above. The random number of the subject will be generated by the randomization statistician using the stratified block randomization method. Randomization stratification factors include presence of a high-risk factor of progression to severe illness, and COVID-19 vaccination status (incomplete basic immunization, completed basic immunization, completed booster immunization). 1200 subjects will be randomized in a 1:1 ratio into the investigational drug group or placebo group.

The drug codes of this trial will be generated and packaged according to the actual required drug quantity. The drug number and its association with the actual grouping will be imported into the Interactive Web Response System (IWRS) system by the drug administrator prior to subject randomization. The subject random allocation table is imported into the IWRS system by the randomization statistician, and the clinical study participants are blinded to the subject random assignment table. After successful screening of a subject, the IWRS will be used to assign random number and drug number to the subject. No matter whether the randomized subjects use the study drug or not, if the subjects are terminated for any reason, their random numbers cannot be assigned to other subjects for reuse.

4.2.2 Blinding and its implementation

During the treatment period, the packaged study drug will be provided in a double-blind way to maintain the double-blind nature of the study. The sponsor, investigators and other personnel involved in the assessment and implementation of the trial will not be aware of the distribution of therapeutic drugs.

The sponsor or its designee will blind the investigational drug and placebo. Once a subject proves eligible after screening, the investigator will give corresponding drugs to the subject according to the drug number.

4.2.3 Principle for emergency unblinding

Neither the investigators nor other clinical observers may attempt to know which study drug the subject is being treated with. If an emergency occurs or the subject needs to be rescued and it is necessary to know what kind of treatment the subject is receiving, the investigator should contact the principal investigator and the sponsor to jointly decide whether to perform emergency unblinding. In extreme emergencies, emergency unblinding can be performed at the discretion of the authorized investigators. After the emergency has been eliminated or controlled, the investigator of the site should inform the principal investigator and the sponsor of the details in time (suggested to be within 24 hours).

Emergency unblinding should be applied for by an authorized investigator on the randomization system, and the investigator should record the personnel, reasons and time for the emergency unblinding.

After emergency unblinding, the investigator could take corresponding measures to treat or take appropriate care according to routine experience. The subject should withdraw from this study and the investigator should record the reason for withdrawal.

4.3 Study Procedures and Periods

4.3.1 V1: Screening period (D-5 to D1)

Steps to be completed at V1 include:

(1) Signing of the ICF;

(2) Assignment of screening number;

(3) Collection of demographic data, past medical history, surgical history, prior/concomitant medications, and COVID-19 risk factor assessment;

(4) Measurement of height and weight, and calculation of body mass index (BMI);

(5) Vital signs, oxygen support and physical examination;

(6) Pathogenic tests;

(7) Laboratory tests, including hematology, blood biochemistry, urinalysis, and C-reactive protein (CRP) test; see Appendix 6 for the specific items included;

(8) Urine pregnancy test (only for women of childbearing potential, see Appendix 3 for the definition of "women of childbearing potential");

(9) Qualitative SARS-CoV-2 nucleic acid testing (results within 5 days prior to randomization are acceptable, a Ct value of < 35 of the RT-PCR result of N gene or ORF gene of SARS-CoV-2 must be required within 48 h prior to randomization);

(10) Quantitative test of SARS-CoV-2 nucleic acid;

(11) Influenza virus detection;

(12) SARS-CoV-2 immunoglobulin M (IgM)/Immunoglobulin G (IgG) detection;

(13) 12-lead ECG;

(14) Chest CT;

(15) Assessment of COVID-19-related Symptom Score Scale;

(16) Assessment of WHO Clinical Progression Scale;

(17) Verification of inclusion/exclusion criteria;

(18) Randomization (if applicable);

(19) Recording of concomitant medications and therapies;

(20) Recording of AEs.

4.3.2 V2: Treatment period (D1)

Steps to be completed at V2 include:

(1) Vital signs, oxygen support and physical examination;

(2) Laboratory tests, including hematology, serum biochemistry, urinalysis and CRP. See Appendix 6 for the specific items (if laboratory tests have been performed within 72 hours before the first administration, they may not be repeated on D1);

(3) Detection of SARS-CoV-2 IgM/IgG (if it is positive during the screening period, no more test is required);

(4) Detection of CD3/CD4/CD8, procalcitonin, erythrocyte sedimentation rate and interleukin-6 (IL-6);

(5) Qualitative test of SARS-CoV-2 nucleic acid (if the screening period and D1 are on different natural days, the test should be repeated before D1 first dose);

(6) Quantitative test of SARS-CoV-2 nucleic acid (if the screening period and D1 are on different natural days, the test should be repeated before D1 first dose);

(7) Determination of SARS-CoV-2 virus strain;

(8) 12-lead ECG (to be performed at 0.5-1.5 h after the first dose);

(9) Chest CT examination (if a chest CT examination is performed within 5 days before the first administration, it may not be repeated on D1);

(10) Assessment of COVID-19-related Symptom Score Scale (if the screening period and D1 are on different natural days, the assessment should be repeated before D1 first dose);

(11) Assessment of WHO Clinical Progression Scale (if the screening period and D1 are on different natural days, the assessment should be repeated before D1 first dose);

(12) Verification of inclusion/exclusion criteria (if randomization has been completed during the screening period, it is not applicable on D1);

(13) Randomization (if randomization has been completed during the screening period, it is

not applicable on D1);

(14) Administration;

(15) Dispensing of Subject Diary Card;

(16) Collection of blood sample within 2 h before the first dose and at 0.5 to 1.5 h after the first dose on the same day as PopPK sample (whether to collect or not can be chosen according to the willingness of the subjects);

(17) Recording of concomitant medications and therapies;

(18) Recording of AEs.

Note: D1 is the day for the first dose. If the screening period and D1 are on the same natural day, there is no need for all tests and assessments to be repeated. If they are on different and consecutive days, only the followings need to be repeated before the first dose on D1: qualitative and quantitative SARS-CoV-2 nucleic acid test, assessment of COVID-19-related Symptom Score Scale, assessment of WHO Clinical Progression Scale. Physical examinations, vital signs, and oxygen support are recommended to be repeated prior to D1 dosing, but are not mandatory.

4.3.3 V3: Treatment period (D2, telemedicine visit)

Steps to be completed at V3 include:

(1) Assessment of COVID-19-related Symptom Score Scale;

(2) Assessment of WHO Clinical Progression Scale;

(3) Administration;

(4) Recording of concomitant medications and therapies;

(5) Recording of AEs.

4.3.4 V4: Treatment period (D3, telemedicine visit)

Steps to be completed at V4 include:

(1) Assessment of COVID-19-related Symptom Score Scale;

(2) Assessment of WHO Clinical Progression Scale;

(3) Administration;

(4) Recording of concomitant medications and therapies;

(5) Recording of AEs.

4.3.5 V5: Treatment period (D4)

Steps to be completed at V5 include:

(1) Vital signs, oxygen support and physical examination;

(2) Laboratory tests, including hematology, serum biochemistry, urinalysis and CRP. See Appendix 6 for the specific items;

(3) Detection of CD3/CD4/CD8, procalcitonin, erythrocyte sedimentation rate and IL-6;

(4) Qualitative test of SARS-CoV-2 nucleic acid (if the subject is confirmed to be negative or progresses to severe/critical COVID-19, no sampling is required);

(5) Quantitative test of SARS-CoV-2 nucleic acid;

(6) 12-lead ECG (it is performed according to the willingness of the subject and as assessed by the investigator);

(7) Assessment of COVID-19-related Symptom Score Scale;

(8) Assessment of WHO Clinical Progression Scale;

(9) Collection of blood sample within 2 h before the first dose on the same day as PopPK sample (whether to collect or not can be chosen according to the willingness of the subjects);

(10) Administration;

(11) Recording of concomitant medications and therapies;

(12) Recording of AEs.

4.3.6 V6: Treatment period (D5, telemedicine visit)

Steps to be completed at V6 include:

(1) Assessment of COVID-19-related Symptom Score Scale;

(2) Assessment of WHO Clinical Progression Scale;

(3) Administration;

(4) Recording of concomitant medications and therapies;

(5) Recording of AEs.

4.3.7 V7: Post-treatment assessment period (D7)

Steps to be completed at V7 include:

(1) Vital signs, oxygen support and physical examination;

(2) Qualitative test of SARS-CoV-2 nucleic acid (if the subject is confirmed to be negative or progresses to severe/critical COVID-19, no sampling is required);

(3) Quantitative test of SARS-CoV-2 nucleic acid;

(4) 12-lead ECG (it is performed according to the willingness of the subject and as assessed by the investigator);

(5) Chest CT (only subjects with pneumonia on imaging at baseline);

(6) Assessment of COVID-19-related Symptom Score Scale;

(7) Assessment of WHO Clinical Progression Scale;

(8) Recording of concomitant medications and therapies;

(9) Recording of AEs.

4.3.8 V8: Post-treatment assessment period (D10±1)

Steps to be completed at V8 include:

(1) Vital signs, oxygen support and physical examination;

(2) Qualitative test of SARS-CoV-2 nucleic acid (if the subject is confirmed to be negative or progresses to severe/critical COVID-19, no sampling is required);

(3) Quantitative test of SARS-CoV-2 nucleic acid;

(4) Assessment of COVID-19-related Symptom Score Scale;

(5) Assessment of WHO Clinical Progression Scale;

(6) Recording of concomitant medications and therapies;

(7) Recording of AEs.

4.3.9 V9: Post-treatment assessment period (D14±2)

Steps to be completed at V9 include:

(1) Vital signs, oxygen support and physical examination;

(2) Laboratory tests, including hematology, serum biochemistry, urinalysis and CRP. See Appendix 6 for the specific items;

(3) Detection of CD3/CD4/CD8, procalcitonin, erythrocyte sedimentation rate and IL-6;

(4) Qualitative test of SARS-CoV-2 nucleic acid (if the subject is confirmed to be negative or progresses to severe/critical COVID-19, no sampling is required);

(5) Quantitative test of SARS-CoV-2 nucleic acid;

(6) 12-lead ECG (it is performed according to the willingness of the subject and as assessed by the investigator);

(7) Assessment of COVID-19-related Symptom Score Scale;

(8) Assessment of WHO Clinical Progression Scale;

(9) Recording of concomitant medications and therapies;

(10) Recording of AEs.

4.3.10 V10: Post-treatment assessment period (D21±2)

Steps to be completed at V10 include:

(1) Vital signs, oxygen support and physical examination;

(2) Qualitative test of SARS-CoV-2 nucleic acid (if the subject is confirmed to be negative or progresses to severe/critical COVID-19, no sampling is required);

(3) Quantitative SARS-CoV-2 nucleic acid test (for patients whose symptoms have not recovered, samples can continue to be collected if deemed as necessary by the investigator);

(4) Assessment of COVID-19-related Symptom Score Scale;

(5) Assessment of WHO Clinical Progression Scale;

(6) Recording of concomitant medications and therapies;

(7) Recording of AEs.

4.3.11 V11: Post-treatment assessment period (D28+3 [EOS])

Steps to be completed at V11 include:

(1) Vital signs, oxygen support and physical examination;

(2) Laboratory tests, including hematology, serum biochemistry, urinalysis and CRP. See Appendix 6 for the specific items;

(3) Detection of CD3/CD4/CD8, procalcitonin, erythrocyte sedimentation rate and IL-6;

(4) Qualitative test of SARS-CoV-2 nucleic acid (if the subject is confirmed to be negative or progresses to severe/critical COVID-19, no sampling is required);

(5) Quantitative test of SARS-CoV-2 nucleic acid;

(6) 12-lead ECG (it is performed according to the willingness of the subject and as assessed by the investigator);

(7) Urine pregnancy test (only for women of childbearing potential, see Appendix 3 for the definition of "women of childbearing potential");

(8) Assessment of COVID-19-related Symptom Score Scale;

(9) Assessment of WHO Clinical Progression Scale;

(10) Return subject diary card;

(11) Recording of concomitant medications and therapies;

(12) Recording of AEs.

4.3.12 Early withdrawal (within 7 days after early withdrawal from the study is confirmed)

Steps to be completed at the early withdrawal visit include:

(1) Vital signs, oxygen support and physical examination;

(2) Laboratory tests, including hematology, serum biochemistry, urinalysis and CRP. See Appendix 6 for the specific items;

(3) Detection of CD3/CD4/CD8, procalcitonin, erythrocyte sedimentation rate and IL-6;

(4) Qualitative test of SARS-CoV-2 nucleic acid;

(5) Quantitative test of SARS-CoV-2 nucleic acid;

(6) 12-lead ECG (it is performed according to the willingness of the subject and as assessed by the investigator);

(7) Urine pregnancy test (only for women of childbearing potential, see Appendix 3 for the definition of "women of childbearing potential");

(8) Assessment of COVID-19-related Symptom Score Scale;

(9) Assessment of WHO Clinical Progression Scale;

(10) Return subject diary card;

(11) Recording of concomitant medications and therapies;

(12) Recording of AEs.

4.3.13 Telemedicine visit

The subjects have telemedicine visits on D2, D3 and D5, and do not need to return to the study site. During the post-treatment assessment period, if a subject is unable to return to the study site for an on-site visit, a telemedicine visit may be conducted. In the case of telemedicine visit, the subjects should complete the COVID-19-related Symptom Score Scale every day to record the concomitant medications and treatments and AEs. The investigator will inquire about the subjects' condition by telephone at each visit time and complete the WHO Clinical Progression Scale. Other items will not be performed in the case of telemedicine visits.

4.3.14 Unscheduled visit

The unscheduled visits may be conducted as clinically indicated, and the measures taken by the investigator (including laboratory test results, etc.) should also be recorded in the unscheduled visits of the eCRF.

5. Study Drugs

5.1 General Information of the Study Drugs

Investigational Drug Group

Drug name:	GST-HG171
Dosage form:	Tablet
Description	Pink film-coated tablet, with white or off-white core
Strength:	150 mg
Shelf life:	12 months tentatively
Storage conditions:	Seal and store below 25℃
Manufacturer:	Fujian Cosunter Pharmaceutical Co., Ltd.
Supplier:	Fujian Akeylink Biotechnology Co., Ltd.

Drug name:	Ritonavir
Dosage form:	Tablet
Description	White to off-white oval film-coated tablet, scored "RTV" on one side, with white or off-white core
Strength:	100 mg
Shelf life:	24 months
Storage conditions:	Store at room temperature (below 30℃)
Manufacturer:	Jiangsu Sinotherapeutics Co., Ltd.
Supplier:	Fujian Akeylink Biotechnology Co., Ltd.

Placebo Group

Drug name:	Placebo for GST-HG171
Dosage form:	Tablet
Description	Pink film-coated tablet, with white or off-white core
Strength:	150 mg
Shelf life:	12 months tentatively
Storage conditions:	Seal and store below 25℃
Manufacturer:	Fujian Cosunter Pharmaceutical Co., Ltd.
Supplier:	Fujian Akeylink Biotechnology Co., Ltd.

Drug name:	Ritonavir blank tablet
Dosage form:	Tablet
Description	White to off-white oval film-coated tablet, scored "RTV" on one side, with white or off-white core
Strength:	100 mg
Shelf life:	24 months tentatively
Storage conditions:	Store at room temperature (below 30℃)
Manufacturer:	Ascletis Pharmaceutical (Zhejiang) Co., Ltd.

Supplier:	Fujian Akeylink Biotechnology Co., Ltd.

5.2 Method of Administration

Oral administration. The dosage of GST-HG171 tablets and GST-HG171 tablets placebo is 150 mg/time, BID, for 5 consecutive days. The dosage of ritonavir tablets and ritonavir blank tablet is 100 mg/time, BID, for 5 consecutive days. If the administration starts on the morning of D1, it will end on D5; if the administration starts on the evening of D1, it will end on the morning of D6. The interval time window of study drug administration is 12 h ± 4 h. Drug administration is not affected by meals. If one dose is delayed, it should be taken as soon as possible, but not later than 4 hours before the next dose. If less than 4 hours before the next dose, the drug should not be taken, and the dose should be recorded as missing. The subject should not double the next dose of study drug to make up for the "missing dose".

5.3 Drug Packaging and Labeling

The Fujian Akeylink Biotechnology Co., Ltd. and the contract research organization (CRO) will design labels for all study drugs and perform drug packaging and labeling in accordance with the Good Clinical Practice (GCP) and applicable national regulations.

The drug label should be in a uniform format. The contents of the packaging label of the investigational drug and placebo include: the protocol number, the drug No., the name of the clinical trial drug (indicating "specific for the clinical trial"), the strength, storage, batch number, expiry date, production date, manufacturer, etc.

5.4 Drug Distribution, Recording and Return

All study drugs used in this trial will be provided by the sponsor free of charge, and will be distributed to the study sites as planned. Each clinical study site will appoint a person to be responsible for the reception, custody, distribution, recovery and corresponding recording of study drugs.

The study drugs shall be uniformly preserved, managed and distributed by specially-assigned person in the study site. The person in charge of the study site will confirm in writing that the study drugs have been received and will be used according to the requirements of the protocol. The person in charge of the study site will make records on the reception, distribution and return of study drugs according to the standard operating procedures of the study site.

The investigator or his/her designated personnel must agree not to provide study drugs to any subjects who have not been enrolled into this study, or any physician or scientist who is not authorized for this study.

At the end of the study, the number of study drugs delivered must be consistent with the number of used and destroyed/returned ones, and if there is any inconsistency, it should be recorded and indicated with causes.

6. Concomitant/Prohibited Medications and Therapies

6.1 Concomitant Medications and Therapies

Concomitant medications and therapies, including any drugs and therapies used by the subject from the signing of the informed consent form to the last visit, should be recorded in detail (including the start/end time and purpose of use). All subjects should be asked about their concomitant medications and therapies at each clinical visit.

During the screening period, prior medications should be collected according to the inclusion/exclusion criteria. The investigator will verify the inclusion/exclusion criteria of patients according to the prior medication history. If the inclusion/exclusion criteria are not defined, the investigator should try to collect all drugs used by the subject before screening (especially within one month), including prescription drugs, over-the-counter drugs, and Chinese herbal/patent medicine.

6.1.1 Permitted concomitant medications and therapies

In addition to study interventions and prohibited medications, if subjects progress to severe/critical COVID-19 during the study, they are allowed to be treated in accordance with local guidelines for severe/critical COVID-19, with the exception of drugs prohibited by the package insert of Paxlovid or other drugs or substances highly dependent on CYP3A4, CYP2B6, CYP1A2, MDR1, or OATP1B3 for clearance within 4 days after the last dose of study drug.

Symptomatic treatment

Recovery of COVID-19-related symptoms is the primary endpoint of this study. If the relevant symptoms in the subject are mild, no intervention is required unless necessary, and it is recommended to observe the symptoms for 1-2 days first; if the subject remains intolerable and strongly requests medication, drug intervention can be considered as described in Appendix 8, but should be avoided whenever possible.

If any medication for symptomatic treatment is used, the dosage, date and time of each dose should be recorded. Measurement of body temperature and assessment of COVID-19 symptoms will be performed before or more than 4 hours after symptomatic treatment.

The investigator should determine whether or not to use other concomitant medications or therapies on the premise of guaranteeing subjects' interests and safety. All concomitant medications and therapies should be specified in the eCRF and the reasons for medication should be described. From the signing of the informed consent form to the whole study treatment period, any new concomitant medications/therapies, or change of concomitant medication dose, as well as the reason for medication, the date of administration (including the start and end dates) and dose information (including dose, route and frequency) must be recorded in the corresponding part of the eCRF.

6.1.2 Prohibited concomitant medications and therapies

- Subjects are prohibited from antiviral therapies against SARS-CoV-2 (e.g., Paxlovid, Molnupiravir, Azvudine, Simnotrelvir Tablets/Ritonavir Tablets, Deuremidevir Hydrobromide Tablets, etc.) within 14 days prior to randomization through Day 28 of the study;
- Subjects are prohibited from COVID-19 monoclonal antibody, intravenous injection of COVID-19 human immunoglobulin, or COVID-19 convalescent plasma therapy within 30 days prior to randomization or within 5 drug half-lives (whichever is longer) until D28 of the study;
- Subjects are prohibited from medications for the alleviation of COVID-19 symptoms from randomization to Day 28 of the study: antipyretics/analgesics, antitussives/expectorants, combination cold remedies, antihistamines**, antibacterials and antifungals (except for complications of suspected bacterial or fungal infection after Day 1 treatment), glucocorticoids**, immunosuppressants, Chinese herbal/patent medicines that have an adjunctive mitigating effect on COVID-19 symptoms, except for medications permitted in the *Medication Guide for Symptom Alleviation During the Study* (see Appendix 8).

*Note: **The use of skin preparations is allowed, but they should not be used in the eyes, nose or ears or by inhalation.*

- Subjects are prohibited from receiving traditional Chinese medicine (e.g., acupuncture) or traditional Chinese medicine physiotherapy (e.g., cupping) to relieve COVID-19 symptoms from randomization to Day 28 of the study.
- Subjects are prohibited from using other investigational drugs within 3 months prior to administration through Day 28 of the study.
- Subjects are prohibited from use of drugs prohibited by the package insert of Paxlovid or any other drugs or substances (Appendix 4) that are highly dependent on CYP3A4, CYP2B6, CYP1A2, MDR1 or OATP 1B3 for clearance during study drug administration and within 4 days after the last dose.
- Subjects are prohibited from concomitant medications of any potent CYP3A4 or MDR1 inducers within 28 days prior to randomization and during the treatment of study drug until 4 days after the last dose (Appendix 4).

Note: For drugs not listed in Appendix 4, co-administration should not be assumed as safe. Investigators will review all concomitant medications prior to the first dose to determine if they are potent CYP3A4 or MDR1 inducers or are highly dependent on CYP3A4, CYP2B6, CYP1A2, MDR1, or OATP1B3 for clearance, which will be prohibited.

6.2 Subject Compliance

During conversation of informed consent, the investigators must emphasize the compliance to subjects. During the process of the trial, if the subjects have poor compliance, the investigator should find the cause and actively take corresponding measures (e.g., emphasizes the importance of protocol compliance to subjects), and completely record the related non-

compliance, cause and corresponding measures taken.

7. Assessment of Study Endpoints

7.1 Efficacy Endpoint Assessment

7.1.1 Qualitative test of SARS-CoV-2 nucleic acid

Samples are collected according to the visit schedule in the Schedule of Activities and nasopharyngeal/oropharyngeal swab testing is acceptable during the screening period (results within 5 days prior to randomization are acceptable, a Ct value < 35 of the RT-PCR result of N gene or ORF gene of SARS-CoV-2 must be required within 48 h prior to randomization), and nasopharyngeal swabs were collected at follow-up visits. If the subject is confirmed to be negative or progresses to severe/critical COVID-19, no sampling is required. The investigator can adjust the specific test items and timing according to the patient's condition during the study. Confirmed negative conversion is defined as two consecutive negative SARS-CoV-2 nucleic acid tests (at least 24 hours apart). If the negative conversion is not confirmed by nucleic acid test, it is recommended to continue sampling. If the subject is unable to return to the hospital for follow-up, a telemedicine visit can be conducted on D7 or later, and the formal qualitative nucleic acid result with Ct value in an external hospital is acceptable.

7.1.2 Quantitative test of SARS-CoV-2 nucleic acid

Nasopharynx swab samples should be collected according to the visit schedule in the Schedule of Activities, and SARS-CoV-2 RNA should be analyzed by RT-PCR. See the Standard Operating Procedure of the central laboratory (see *Laboratory Operation Manual*) for specific sample collection, handling, transportation, storage and testing methods. Baseline SARS-CoV-2 nucleic acid test is defined as the test result before the first dose on D1; if there was no sampling on D1, the test result obtained at the time that is the closest to D1 during the screening period would be used as the baseline. D21: It is recommended to continue sampling regardless of symptom recovery or confirmed negative conversion of nucleic acid test. Sampling is not required if it is a telemedicine visit.

7.1.3 Chest CT

Optional to proceed as indicated by clinical requirements or other medical needs. D1: Assessments before administration are considered as baseline values. If chest CT examination is performed within 5 days before the first administration, it may not be repeated on D1. For subjects with baseline imaging findings of pneumonia, reassessment is performed on D7 as a secondary efficacy endpoint; for subjects without baseline imaging findings of pneumonia, reassessment is not required on D7. Changes on D7 relative to baseline, including no change, deterioration, and improvement should be assessed by the investigator.

7.1.4 Assessment of COVID-19-related Symptom Score Scale

Subjects should complete the COVID-19-related Symptom Scoring Scale every day, including 11 target symptoms and other COVID-19 symptoms (see Appendix 1 for details). At least 2 COVID-19 target symptoms occur within 72 hours prior to randomization, including 1

designated symptom: fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath, or difficulty breathing. The symptom scoring on D1 should be completed prior to the first dose, and the COVID-19-related Symptom Score Scale should be completed at approximately the same time each day thereafter. The subject should score according to the worst severity of each symptom in the past 24 hours. Subjects may fill in the score scale under the guidance or assistance of the investigator. If it is a telemedicine visit, the investigator is to instruct the subject to complete it via telephone.

7.1.5 Assessment of WHO Clinical Progression Scale

The investigator should complete the WHO Clinical Progression Scale (see Appendix 2 for details) after inquiring the subject. The scale scoring on D1 should be completed by the investigator prior to the first dose, and the WHO Clinical Progress Scale should be completed at approximately the same time for each visit thereafter. The investigator should score according to the worst severity of the subject in the past 24 hours. In case of telemedicine visit, the investigator will call the subject every visit to inquire about the subject and complete the WHO Clinical Progression Scale in a timely manner.

7.2 Safety Endpoint Assessment

7.2.1 Physical examination

Thorough physical examination including: general condition, head and neck, lymph nodes, skin, chest, abdomen, and musculoskeletal system (including extremities and the spine), and nervous system.

Simple physical examination including but not limited to: general condition, abdomen, and any other abnormal signs which should be noted at the discretion of the investigator.

A thorough physical examination is conducted during the screening period and simple physical examination is conducted as indicated by the subject's status and standard of care during the study.

7.2.2 Vital signs and oxygen support

Including temperature, pulse rate, blood pressure, respiratory rate, SpO_2 and inspired oxygen flow (if applicable), fraction of inspired oxygen (FiO_2) (if applicable), mode of oxygen delivery (if applicable), and oxygen support procedures (if applicable). The investigator can adjust the specific test items according to the patient's condition. The blood pressure and pulse should be measured after the subject has rested for at least 5 minutes.

7.2.3 12-ECG

ECG is performed at the site visit only for the first 100 subjects (sentinel cohort) as indicated in the flow chart. ECG may be continued for subjects enrolled after the sentinel cohort as recommended by the DSMB. ECG should be performed after the first dose on D1, and the recommended time window is 0.5-1.5 h after administration. ECG at subsequent visits can be

conducted according to the willingness of the subject and as assessed by the investigator without specific requirements. Based on the results of the second interim analysis, a determination can be made as to whether the subsequent subjects enrolled need to continue the ECG. All planned ECG examinations should be performed after the subject has rested for at least 5 minutes. Heart rate, PR interval, RR interval, QT interval, QRS interval and QTcF should be recorded (see Appendix 5 for calculation method). If ECG abnormality is found, the investigator and/or authorized study personnel can decide whether to retest according to the clinical situation of the subject and assess the examination results. An unscheduled visit can also be arranged for ECG examination if clinically indicated.

7.2.4 Clinical laboratory tests

The investigator must evaluate all values beyond the normal range (CS: clinically significant; NCS: non-clinically significant), and sign and date. If the investigator judges that an abnormal value is clinically significant and meets the definition of AEs, it should be recorded as an AE. In this study, the investigator can decide whether additional or repeated examination is required according to the actual situation of the subject.

If the items that appear in the laboratory test report according to the laboratory's operating specifications but are not required in the trial protocol (such as some parameters in hematology), they do not need to be recorded in the eCRF. See Appendix 6 for the specific contents of the laboratory tests.

7.2.5 Pregnancy test

During the screening period and at the last visit, urine pregnancy tests should be conducted in the local laboratory for women of childbearing potential (see Appendix 3). During the study period, the serum pregnancy test may be added at the investigator’s discretion.

7.3 PK Sampling

PK blood samples may be collected based on the subject’s willingness. The collection time points include: within 2 hours before the first dose on D1, 0.5-1.5 hours after the first dose on D1, and within 2 hours before the first dose on D4. Sampling can be performed as appropriate for the actual situation. It is encouraged to at least collect the blood sample within 2 hours before the first dose on D4. If the PK blood sample is not collected , it may not be regarded as a protocol deviation. Blood samples will be collected with EDTA blood collection tubes, about 4 mL each time.

8. Adverse Event

8.1 Definitions

8.1.1 Adverse events

AEs refer to all adverse medical events that occur after subjects receive the study drug, which can be manifested as symptoms, signs, diseases or laboratory test abnormalities, but are not necessarily related to the study drug. AEs are therefore any untoward or unexpected symptoms, signs or diseases, including adverse drug reactions, important laboratory abnormal values, new diseases occurring during the study period and aggravated pre-existing diseases or symptoms (except disease proposed to be treated with the study drug).

An AE does not include the following:

- Any pre-existing disease, condition, or laboratory abnormality present or detected prior to the screening that does not worsen further;
- Circumstances where no adverse medical events have occurred (e.g., admission due to elective surgery, social reasons and/or personal convenience);
- Any medical condition or clinically significant laboratory abnormality occurring after signing of the informed consent form and prior to the first dose and unrelated to a protocol procedure is not considered as an AE, but is considered as pre-existing. It should be recorded into medical history.

8.1.2 Serious adverse event

An SAE refers any of the following adverse medical events experienced by a subject who has received the study drug (at any dose):

- Leading to death;
- Life threatening;

Note: "life-threatening" in SAE refers to that subjects are in the immediate risk of death from the adverse event as it occurs, it does not include an event that, has it occurred in a more severe form, might have caused death.

- Requiring hospitalization or prolonged hospitalization;

Note: Complications that occur during hospitalization are AEs. If the complication causes an extension of the current hospitalization or meets other SAE criteria, the event should be considered as an SAE. Hospitalization for selective treatment of current symptoms without aggravation from baseline should not be considered as an AE.

- Persistent or serious disability or incapacity;

Note: The term "disability" means that the subject's activities of daily living are substantially impaired.

- Congenital anomaly or birth defect;
- Other important medical events.

Medical and scientific judgment must be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may be considered serious if medical intervention is necessary to prevent one of the above situations. For example, intensive therapy administered due to allergic bronchospasm in the emergency room or at home; blood dyscrasia or convulsion not resulting in inpatient hospitalization; or those leading to drug dependence or drug abuse.

The terms "severe" and "serious" are not synonyms. The term "severe" is often used to describe the degree (severity) of a specific event, referring to the intensity of AEs (Common Terminology Criteria for Adverse Events [CTCAE] V5.0 grading, see Section 8.3 for details); the medical significance of the event itself may be relatively small (e.g., severe headache without any further findings). The severity and seriousness of each AE should be independently assessed and recorded in the eCRF.

If an event is not judged as an AE according to the above definition, it cannot be judged as an SAE even if it meets the "serious" conditions (for example, hospitalization due to signs/symptoms of the study disease, and death due to disease progression).

8.1.3 Suspected unexpected serious adverse reactions

Suspected unexpected serious adverse reactions (SUSARs) refer to suspected and unexpected serious adverse reactions whose clinical manifestations are beyond the Investigator's Brochure for the study drug, package inserts for marketed drugs, summary of product characteristics and other existing information in terms of their nature and severity.

8.2 Causality

The investigator should make a comprehensive analysis based on the specific situation of the subject's AE and past medical history, concomitant diseases and concomitant medications to judge the causal relationship between the AE and the study drug. The investigator should perform causality analyses for treatment-emergent symptoms in order to identify potential correlations between the AE and the study drug.

The causal relationship between the AE and study drug is classified as definitely related, probably related, possibly related, possibly unrelated and definitely unrelated. Among them, "definitely related, probably related, possibly related" are classified as related to the study drug, and such AEs are considered as study drug-related AEs. For AEs that are possibly unrelated, the sponsor's medical team should timely communicate with the investigator, confirm the basis on which the AE is judged as unlikely related, and record it in detail. "Possibly unrelated, definitely unrelated" are classified as not related to the study drug.

Definitely	There is clear evidence that there is a causal relationship between the AE and the study

related	drug, and the impact of other factors can be excluded. ● There is reasonable temporal relationship between onset of AE and use of the study drug; ● The occurrence of the AE cannot be explained by the subject's own diseases, concomitant medications or other factors; ● The occurrence of the AE is determined pharmacologically or phenomenologically; ● There is a reasonable response (the AE relieves or disappears) after de-challenge (drug withdrawal or dose reduction); ● If necessary, the re-challenge (resumption of administration or dose increase) result is positive.
Probably related	There is evidence that there is a causal relationship between the AE and the study drug, and the AE is unlikely to be caused by other factors. ● There is reasonable temporal relationship between onset of AE and use of the study drug; ● The occurrence of the AE is unlikely to be attributed to the subject's own diseases, concomitant medications or other factors; ● There is a reasonable response (the AE relieves or disappears) after de-challenge (drug withdrawal or dose reduction); ● The re-challenge (resumption of administration or dose increase) result is not required.
Possibly related	There is some evidence that there is a causal relationship between the AE and the study drug (for example, there is a reasonable temporal relationship between the occurrence of the AE and the use of the study drug), but other factors (for example, the subject's own diseases, concomitant medications) may also promote the occurrence of this event. The de-challenge (drug withdrawal or dose reduction) result can be missing or unclear.
Possibly unrelated	From the temporal relationship between the occurrence of AE and the use of the study drug, the causal relationship between the two is unlikely, and the subject's own diseases, concomitant medications or other factors provide a more reasonable explanation.
Definitely unrelated	The occurrence of the AE is completely independent of the use of the study drug (for example, the AE occurs before the use of the study drug), and/or there is evidence that the AE is definitely related to other factors (at this time, another clear cause must be recorded).

8.3 Criteria for Assessing the Severity of AEs

The severity of AEs is evaluated according to CTCAE 5.0:

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

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

Grade 3: Serious or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden);

Grade 4: Life-threatening, urgent intervention indicated;

Grade 5: AE-related death.

8.4 Study Drug-related Actions

- Permanent drug discontinuation - The study drug is discontinued because of a specific AE.
- Dose unchanged - The study drug does not need to be discontinued for a specific AE.
- Unknown - Only used when the action taken cannot be determined.
- Not applicable - The study drug is discontinued for reasons other than a specific AE, for example, the study is terminated, the subject dies, or the study drug has been discontinued before onset of the AE.
- Dose interruption - Temporary interruption (suspension) (including the subject's active interruption of the drug) of the study drug due to a specific AE, and then resume the drug afterwards.

8.5 Description of Outcome of Adverse Event

- Recovered/resolved: "AE/SAE end date" should be specified".
- Recovering/resolving: the event is not completely resolved, but the subject is recovering. Follow-up visits are required.
- Not recovered/unresolved: The event is ongoing.
- Recovered/resolved with sequela: Only when the subject will have sequela lasting for a long time or lifetime, the "AE/SAE end date" should be indicated.
- Fatal: When death occurs due to an AE, time of death has to be recorded.
- Unknown: The investigators cannot learn about the AE, e.g., the subject is lost to follow-up.

If the outcome of an AE is assessed as "recovering/resolving" or "not recovered/unresolved" or "unknown", the AE end date is not required to be recorded temporarily.

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

8.6 Collection, Recording and Reporting of AEs

8.6.1 Collection and reporting of AEs

AE collection period

From the definition of AEs/SAEs, only adverse medical events occurring after the use of the study drug are called "AEs/SAEs". However, for the purpose of collecting "safety information" in the clinical trial, the adverse medical events that occur after the subject sign the ICF should all be collected and recorded until the last visit (Day 28 of the study or early withdrawal).

Regardless of its severity or relationship with the study drug, it should be recorded on the corresponding page of the original medical record and eCRF. Adverse medical events that are considered by the investigator to be COVID-19 complications or COVID-19-related progresses do not need to be recorded as AEs.

Clinical adverse events that occur from the signing of the ICF by the subject to pre-dose of the first dose are recorded in the electronic Case Report Form (eCRF) as medical history/concomitant diseases and are not recorded as AEs/SAEs unless one of the following conditions is met: injury/damage caused by any clinical laboratory test operation (AEs related to study operating procedures); AEs caused by drug discontinuation associated with the study protocol; AEs caused by a drug other than the investigational drug taken as part of the treatment regimen. Adverse medical events that occur during the study treatment period and post-treatment assessment period should be recorded as AEs. If the severity meets the seriousness criteria for SAEs, they should be recorded as SAEs. The initial AE grade should be recorded and updated when the AE grade changes. The AE grade change process should be recorded in detail.

In order to ensure the safety of subjects, the investigator should take appropriate measures to track all AEs until the AE is recovered, stable, or otherwise explained, or the subject is lost to follow-up. This means that observation may still be required after the last visit according to the protocol.

AE reporting

At each study visit, the investigator will assess whether there is a subjective AE. A neutral question can be asked, such as "How do you feel since the last visit?". The subject can report AEs occurring at any other time during the study. AEs occurring in all subjects, whether related to the use of the study drug or not, should be followed up to normal or remission, or recovery to the baseline level, or the investigator decides that no further follow-up is needed, or the subject is lost to follow-up. All AEs will be recorded on AE page of eCRF, whether the investigator considers the event related to study treatment or not.

For the reporting of AEs, a single diagnosis or syndrome rather than a certain symptom should be used to describe AEs as far as possible. The investigator should record in detail the start date and end date of AE symptoms, the severity of AE and its seriousness criteria (applicable to SAEs, meeting the judgment criteria for SAEs), the assessment of the correlation between AE and the study drug or study procedure, the action taken with the study drug, the treatment given to AE, and the outcome of AE.

Subject's diary will not be used as main methods to collect AE. However, if the investigator identifies a potential AE through these documents, the subject should be followed up appropriately for medical evaluation. Through this follow-up, if any AE not previously reported is confirmed, it should be reported according to normal reporting requirements.

8.6.2 Collection and reporting of SAEs

For all SAEs that occur within the collection time limit specified in this protocol, the investigator must fill in, sign and date the SAE Report Form within 24 hours of awareness, immediately report it to the sponsor (the E-mail is as follows) or the CRO appointed by the sponsor, and take appropriate treatment measures for the subject in a timely manner.

Email of the sponsor: pv@akeylink.cn

zhangtingting@akeylink.cn

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

In case of reports involving death events, the investigator should provide the sponsor and Ethics Committee with other necessary information, such as autopsy report and final medical report.

8.7 Suspected Unexpected Serious Adverse Reaction Report

The sponsor and/or the sponsor's representative should comprehensively analyze, evaluate and judge the safety information received of any sources in a timely manner, including severity, correlation with the study drug and whether it is an expected event, as well as report in an expedited manner depending on the nature (category) of the event within the time limit specified by the regulatory authorities. The sponsor and/or the sponsor's representative should expeditely report SUSARs to all investigators and clinical trial institutions participating in the study, Ethics Committee, drug regulatory authorities and health authorities within specified time limit. The specific expedited reporting standard and procedure are provided in "Standard and Procedure for Expedited Reporting of Safety Data during Drug Clinical Trials" and "Common Q&As on Standard and Procedure for Expedited Reporting of Safety Data during Drug Clinical Trials (Version 1.0)", released by Center for Drug Evaluation, National Medicinal Products Administration (NMPA).

SAEs occurring from the last dose of the study drug to Day 28 of the study still need to be reported. The investigator should report SAEs occurring in the period from the end of the clinical trial or follow-up to the date of obtaining evaluation and approval conclusion to the applicant. If it is an unexpected SAR, expedited reporting should be carried out.

For the SUSAR report and clinical trial-related safety information provided by the sponsor, the investigator should sign and read it in time, and report to the clinical trial institution and the Ethics Committee.

8.8 Definition of Hospitalization

AEs requiring hospitalization for treatment are considered as SAEs. In general, hospitalization includes admission and treatment, and such adverse event should be considered as an SAE.

If hospitalization is for elective surgery, routine clinical procedure, annual examination, observation, epidemic prevention and control policies or protocol requirement, rather than AE, this is not regarded as an AE, but should be recorded in clinical assessment form and the eCRF.

If an unexpected event occurs during this process, it should be reported as "serious" or "non-serious" AE according to routine criteria.

Note: Hospitalization or prolongation of hospitalization for non-medical reason/convenience or objective of the clinical trial does not meet criteria of medical events, so it should not be regarded as an SAE.

8.9 Pregnancy

If any female subject or the partner of male subject participating in this trial is pregnant or found to be pregnant during the study (from signing of the informed consent form to the last visit), the investigator must fill this information in the pregnancy event form and submit it to the sponsor and/or CRO designated by sponsor. The investigator needs to follow up the pregnancy result to the pregnancy outcome (e.g., termination of pregnancy, delivery).

If the outcome of pregnancy meets the SAE criteria (such as spontaneous abortion, induced abortion for medical reason, stillbirth, neonatal death or congenital malformations), the investigator should report following the SAE reporting procedure and record it on the corresponding AE page in eCRF.

"Spontaneous abortion" includes inevitable abortion and missed abortion.

8.10 Overdose

Drug overdose is defined as the accidental or deliberate administration of a high dose of the drugs (including GST-HG171 and ritonavir) during each administration or gradually, and the dose exceeds the dispensed dose during the study (12 tablets). If there is a difference in drug counting, an overdose can only be determined if it is clear that the subject has taken an excess dose. If the subject cannot explain the difference (unless the investigator has reason to suspect that the subject has taken an additional dose), an overdose cannot be determined.

Any drug overdose in the study, whether an AE occurs or not, should be reported to the sponsor and/or CRO designated by sponsor and recorded in the eCRF. Any AE related to drug overdose should be recorded on the corresponding AE page of the eCRF.

9. Data Management

9.1 Completion and Handover of Original Data and eCRF

This study uses an Electronic Data Capture (EDC) system to collect data. Data management plan: The plan is written by data manager (DM) as a guiding document for the whole data management process, and all data management processes should be operated according to the time, content and method defined therein.

The sponsor or Data Department of CRO is responsible for data management to ensure the authenticity, integrity, privacy and traceability of the clinical study data.

eCRF: According to protocol requirements, data collection forms will be designed, and study procedures, name of data sheet and data items collected will be defined. Meanwhile, instructions for filling out the eCRF will be formed and be provided to study sites for the purpose of filling out the eCRF after reviewed by the sponsor.

All the data in the eCRF are from the original medical records and are filled in by the investigator or his/her designated person. Information completeness and accuracy must be ensured. If there is any error that has to be corrected, revision should be made according to instructions for eCRF completion. EDC system will automatically record the name of data reviser and date of revision.

The database can be locked only after the data in the EDC system is confirmed to be unquestionable after source data verification (SDV), DM review, query and other processing. Before data locking, the investigator needs to confirm with electronic signature.

9.2 Database Design and Establishment

The eCRF is designed in compliance with the requirements for data collection in FDA 21 CFR Part 11, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP and National Medical Products Administration (NMPA) GCP (2020). Interface test will be performed by DM. Testing contents include but are not limited to: page design, setting of the visit period, order of entry forms and order of each data point during the visit, etc. For new uniform resource locators (URLs), URL setting test should be performed, such as accuracy of browse right of different users. The database should be established with reference to Clinical Data Interchange Standards Consortium (CDISC) standard as far as possible.

9.3 Data Entry

The study personnel should collect the data of subjects according to the requirements of GCP and study protocol. Moreover, they are required to complete eCRF in an accurate, timely, complete and standard manner according to completion instructions. The eCRFs are not regarded as source documents.

The data will be entered into EDC database timely by the investigators or personnel designated

by the investigators after the follow-up. The data should be entered in strict compliance with the principle of "entering what you see". After the data are entered into system, any correction to the eCRF will be automatically recorded in the system.

9.4 Data Verification and Testing

Data verification includes logic verification and manual verification.

According to finalized data verification plan, DM will set up data logistic verification program in EDC system.

After data entry in EDC system, if there is any illogical data, logic verification will be started and query triggered. These queries have to be reviewed and answered by the investigator or the person authorized by the investigator. If updated data makes a query of logic verification no longer valid, the data query will be closed by system immediately; if the investigator or the person authorized by the investigator confirms data correctness and provides response, DM has to review the response. If the reason is acceptable, the data query will be closed; if data problem is not resolved, DM can continue adding data inquiry to communicate with the investigator or the person authorized by the investigator until final resolution.

The subject data list/report is generated by programming to support manual data verification throughout the study process. If data had to be clarified/verified/confirmed by the investigator or the person authorized by the investigator, manual query could be added in EDC system. DM should ensure that all queries are resolved before database lock and the investigator has completed electronic signature in EDC system to ensure the integrity and accuracy of subject data in the EDC system.

The logical verification test is performed by DM based on the data verification plan. The EDC system is tested whether or not to correctly execute triggering and closing of doubt prompts as pre-designed. Relevant documents generated during the test will be archived.

9.5 Medical Coding

The sponsor or DM of data department of the CRO company designated by the sponsor is responsible for medical coding of this study. The coding contents include but are not limited to previous medical history, concomitant medications and therapies, and AEs.

The past medical history, concomitant therapies, and AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). The concomitant medications are coded using World Health Organization Drug Dictionary (WHO DD). All dictionaries used are confirmed by the sponsor.

During the coding process, if the data cannot be coded due to inappropriate, inaccurate, ambiguous medical terms provided, DM will ask the investigator to verify and confirm through data queries.

DM should send medical coding report to the sponsor for review.

9.6 Database Locking and Exporting

Database locking can be performed only after all subjects have completed the trial, all data have been entered into the system, DM have cooperated with the project team to complete all cleaning tasks before locking the database according to the data management plan agreed by the project, and the principal investigator, sponsor, statistician and DM have signed the application form. Then DM will lock the data. After locking all data, DM will export data from the system and submit to the statisticians for statistical analysis. Data cannot be re-edited after locking, and problems identified after data locking should be jointly confirmed by the principal investigator, sponsor, statistical analyst and data manager, and can be corrected in the statistical analysis program if unlocking is not deemed necessary. If there are explicit evidence for unlocking, DM will unlock the data after the principal investigator and the sponsor sign a database unlocking confirmation form. Then the data can be updated and all updated contents should be documented. After the update is completed, the database lock process needs to be executed again.

10. Statistical Considerations

10.1 General Principles

Statistical analysis will be calculated using SAS 9.4 software or above.

Subject information, efficacy data, safety data and other study endpoint data will be statistically described by treatment group. The statistics used include the number of cases (number of missing cases), mean (two-sided 95% CI, if necessary), median, standard deviation, minimum and maximum for continuous variables, as well as number of cases (number of missing cases), frequency (two-sided 95% CI, if necessary), and percentage for categorical variables.

Unless otherwise specified, the significance level of the test is two-sided 0.05. $P \leq 0.05$ for inter-group comparison indicated statistically significant inter-group difference.

The missing values in the original data will not be imputed. For sensitivity analysis of efficacy and judgment of the time of occurrence of safety events, the method of processing missing values in the original data should be detailed in the Statistical Analysis Plan (SAP).

Unless otherwise specified, baseline is defined as the last valid measurement data before the first study drug administration after enrollment.

The SAP will be finalized before the database locking. After the database is locked, changes made to SAP will be described in a special section of the Statistical Analysis Report.

10.2 Sample Size

It is assumed that the median time to sustained recovery of clinical symptoms is 8 days for GST-HG171 and 10 days for placebo, then 960 subjects (480 in each group) need to be enrolled in a 1:1 ratio to achieve a power of 90% under the significance criterion with the one-sided of 0.0238 (two interim analyses require partial alpha spent), with 856 subjects expected to achieve sustained clinical symptom recovery. Accounting for a drop-out rate of about 20%, 1200 subjects are temporarily planned to be enrolled in this Phase II/III study, with 600 each in the investigational drug group and the placebo group.

10.3 Statistical Analysis Populations

Full Analysis Set (FAS): All randomized subjects who have received at least 1 dose. Subjects will be analyzed according to their randomized groups.

Modified Intent-to-Treat Analysis Set (mITT): Subjects in the FAS who are confirmed to be positive for SARS-CoV-2 nucleic acid by RT-PCR Fleming will be used to control class I errors (α at baseline and non-positive for influenza virus and have at least 1 visit from post-baseline to Day 28. Subjects will be analyzed according to their randomized groups.

Note: Baseline SARS-CoV-2 nucleic acid test is defined as the test result before D1 treatment; if there was no sampling on D1, the test result obtained at the time that is the closest to D1 during the screening period would be used as the baseline.

Per-Protocol Analysis Set (PPS): Subjects in mITT with those have major protocol deviations that may affect the primary efficacy analysis excluded. Protocol deviations will be reviewed at the blinded review meeting and a list of PPS subjects will be generated. The PPS will be determined prior to unblinding.

Safety Analysis Set (SS): All subjects who have received at least 1 dose. Subjects will be analyzed according to the actual treatment received.

Pharmacokinetic Analysis Set (PKS): All enrolled subjects who have received at least 1 dose of study drug, have at least 1 evaluable concentration after administration at the planned PK time point, and have no major protocol violation that may significantly affect PK assessments.

10.4 Statistical Analysis Method

10.4.1 Subject disposition

The information of subjects who have failed screening will be described, including the number of screened cases, number of screen failures, and reasons for screen failures.

The number of cases (percentage) is used to describe the enrollment, completion and withdrawal of the subjects, as well as the reasons for withdrawal.

The inclusion of subjects in each analysis set will be summarized.

10.4.2 Demographic data and baseline characteristics

Demographic data and baseline parameters will be analyzed based on the FAS. The demographic variables and baseline characteristics will be summarized by treatment group.

Continuous variables will adopt descriptive statistics (number of subjects, mean, and standard deviation, minimum, median and maximum). In terms of categorical variables, the frequency and percentage rate will be calculated.

Details will be described in the SAP.

10.4.3 Efficacy analysis

All statistical tests are subjected to two-sided tests. $P \leq 0.05$ indicates a statistically significant difference (unless otherwise specified).

Quantitative variables will be described by mean, standard deviation, median, minimum, maximum, 1st quartile (Q1), and 3rd quartile (Q3). Categorical variables will be presented with number of cases and percentages by category.

The comparison of the general profiles between the two groups will be analyzed using appropriate methods according to the types of variables. The group t test or Wilcoxon rank sum test will be used for the comparison of quantitative variables between groups, the chi-square test or exact probability method will be used for categorical variables, the Wilcoxon rank sum test or CMH test will be used for rank variables, and the log-rank test will be used for time to event variables.

Efficacy data will also be tabulated in detail.

The primary estimand is defined as follows:

Target population: patients with positive SARS-CoV-2 RT-PCR test results and non-positive influenza virus test results, accompanied by at least two COVID-19 target symptoms (COVID-19 target symptoms include fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, and vomiting), including at least one designated symptom (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing), other requirements are listed in inclusion and exclusion criteria.

Treatment: Oral administration of GST-HG171 plus ritonavir or placebo for GST-HG171 plus ritonavir blank tablet as required by the protocol for 5 consecutive days.

Primary efficacy endpoint: Time to sustained recovery of clinical symptoms within 28 days after treatment. Sustained recovery of clinical symptoms is defined as with the score of 0 for all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) for 2 consecutive days. Time to sustained recovery of clinical symptoms is defined as the number of days from the first dose after randomization to the first day when all COVID-19-related target symptoms (fever, cough, congestion or runny nose, sore throat or dry throat, shortness of breath or difficulty breathing, headache, muscle or body aches, diarrhoea, chills, nausea, vomiting) are scored 0 for 2 consecutive days.

Intercurrent events and handling strategies:

Intercurrent event name	**Handling strategy**
Use of prohibited medications or therapies that affect the efficacy endpoints* (see definition in Section 6.1.2)	Adopt combination strategy: for use of prohibited medications or therapies before recovery, treat as unrecovered and censor at 28 days
Use of concomitant drugs other than prohibited medications or therapies that affect the efficacy endpoints*	Use of therapy strategy
Early withdrawal from treatment: (1) Early discontinuation of treatment due to AE (2) Poor medication compliance (< 80%)	Use of therapy strategy
Early withdrawal from treatment: (1) Progressed to severe/critical COVID-19 (2) The efficacy is poor as assessed by investigators	Adopt combination strategy: patients who progressed to severe/critical COVID-19 before recovery or were assessed by investigators as having poor efficacy and were withdrawn from treatment early were treated unrecovered and censored at 28 days
Delayed or interrupted administration due to AE	Use of therapy strategy
Death	Adopt combination strategy: for death before recovery, treat as unrecovered and censor at 28 days

*Prohibited medications or therapies that affect the efficacy endpoints will be identified at the

data review meeting.

Population level summary: Kaplan-Meier method will be adopted to calculate the median time to sustained recovery of clinical symptoms, time to 25% recovery, and time to 75% recovery as well as the corresponding two-sided 95% confidence intervals at the time of three sites in two groups, and Kaplan-Meier curves are drawn. Compare the time to sustained recovery of clinical symptoms between the two groups of subjects using the log-rank test adjusted for randomization factors. Cox regression model will be adopted to calculate the hazard ratio (HR, investigational drug group/control group) of sustained recovery of clinical symptoms corrected by randomization factors and its two-sided 95% confidence interval by taking study grouping and randomization factors as independent variables and condition of and time to sustained recovery of clinical symptoms of subjects as dependent variables.

In order to assess the robustness of the primary analysis results, the following sensitivity analysis is initially planned, which will be further refined in SAP subsequently:

- Compare the time to sustained recovery of clinical symptoms between the two groups of subjects using the uncorrected log-rank.
- Cox regression model will be adopted to calculate the hazard ratio (HR, investigational drug group/control group) of sustained recovery of clinical symptoms and its two-sided 95% confidence interval by taking study grouping as independent variables and condition of sustained recovery of clinical symptoms and time to sustained recovery of clinical symptoms of subjects as dependent variables.
- For the concomitant events "Use of prohibited medications or therapies that affect the efficacy endpoints", "withdrawing from treatment early due to progression to severe/critical COVID-19", "poor efficacy as assessed by the investigator" and "death", patients will be censored on the same day when the concomitant events occurred.
- For the missing values without concomitant events, censoring is at 28 days.
- In addition to sensitivity analysis, this study also preliminarily plans to do the following supplementary analysis, which will be further improved in SAP:
- Adopt different management strategies ("therapy strategies") for concomitant events "Use of prohibited medications or therapies that affect the efficacy endpoints", "withdrawing from treatment early due to progression to severe/critical COVID-19", "poor efficacy as assessed by the investigator" and "death".
- Perform the same analysis as the primary analysis based on the FAS analysis set.
- Perform the same analysis as the primary analysis based on the PPS analysis set.
- Considering the actual possible imbalance of other covariates and thinking that they may potentially affect the evaluation of the treatment effect, in the stratified COX regression model of the primary analysis, other covariates considered as necessary by the project team

will be included.

10.4.4 Safety data analysis

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (the latest version will be used for statistical analyses), and descriptive statistical analysis will be conducted by System Organ Class (SOC)/Preferred Term (PT). The incidences of AEs, treatment-emergent adverse events (TEAEs), study drug-related AEs, and SAEs will be calculated overall and by SOC/PT. The incidences and number of TEAEs and study drug-related AEs will be summarized by SOC and severity. AEs, TEAEs, study drug-related AEs, SAEs, etc. will be tabulated in detail.

For laboratory tests, shift tables will be generated to display normal/abnormal changes before and after administration. Laboratory test results will be tabulated in detail.

For ECGs, shift tables will be generated to display normal/abnormal changes before and after administration. ECG results will be tabulated in detail.

The results of each variable of vital signs and physical examination at each visit will be presented using descriptive statistics and tabulated in detail. See General Principles for analytical methods.

10.4.5 PK analysis

Based on the obtained blood concentration data, a PopPK model of GST-HG171 will be constructed using a nonlinear mixed effect model, and the effect of internal/external factors on the PK characteristics of GST-HG171 will be assessed. If the data permits, the individual exposure parameters of patients will be estimated based on the parameter estimates of the established final PK model for further dose-response (exposure-response) analysis, including an exploratory analysis of the correlation of exposure/efficacy and exposure/safety.

The specific analysis method of PopPK above is shown in the separate PopPK analysis plan, and the analysis results will be provided in a separate report separated from the clinical summary report.

10.4.6 Interim analyses

The sentinel cohort safety review and preliminary efficacy observation (first interim analysis) are planned to be performed to review the sentinel cohort data and make a summary in an unblinded mode after approximately the first 100 sentinel cohort subjects have completed study drug treatment, received drug administration, and completed the D10 study visit assessments. Enrollment of subjects will be continued during the DSMB review of sentinel cohort data, but the study may be suspended or terminated as recommended by the DSMB.

The second interim analysis will be performed when about 60% of the subjects complete the D28 assessment. In this interim analysis, unblinded sample size re-estimation/futility analysis will be conducted. Based on the conditional power, if the interim analysis results fall in the

expected interval (conditional power between 50% and 80%), the sample size will be increased by 480 at most, resulting in the total sample size in the primary analysis set mITT to approximately 1440 cases. The Cui, Hung, and Wang's weighted test statistic will be used to control the Type I error rate as the sample size increases. The specifics of sample size re-estimation will be provided in the interim analysis plan, and an unblinded team will be established to draft the interim analysis plan and complete the interim analysis tasks. The interim analysis will support DSMB to provide recommendations for the implementation of the study:

(1) In case of significant safety issues, the DSMB recommends the sponsor to terminate the trial.

(2) If the termination criteria due to ineffectiveness are met according to the analysis results, the trial can be terminated. The conditional power for estimating the proposed termination criteria due to ineffectiveness based on the analysis results is < 5%.

(3) If the conditional power for estimation based on the analysis results is between 50% and 80%, it is recommended to continue the study on the basis of increasing the number of target events, and conduct the final analysis when the updated number of target events is reached (the significance criterion is two-sided 0.0476).

(4) Otherwise continue the trial with the original planned sample size

Type I error spending calculated by SAS software for sentinel cohort data review (first interim analysis), second interim analysis, and final analysis is shown in the table below.

Analysis	Information proportion	Two-sided Type I error spending
Sentinel cohort data review (first interim analysis)	10%	<0.00001
Second Interim Analysis	60%	0.00762
Final Analysis	100%	0.0476

*The information proportion in the sentinel cohort data review (the first interim analysis) is the proportion of the primary analysis population accounting for 960 subjects; the information proportion of the second interim analysis is the proportion of the primary analysis population accounting for 960 subjects with sample size adjustment.

**In case that the actual cumulative proportion of information is inconsistent with the original plan, the type I error spending will be calculated based on the actual proportion of information.

10.4.7 Final analysis

The final analysis will be conducted after the last visit of the last subject.

10.4.8 Subgroup analysis

In this study, gender, age (≤ 65 years vs. 65-75 years vs. > 75 years), mild vs. moderate, and COVID-19 vaccination or not are considered initially for subgroup analysis, which will be further refined in SAP.

Detailed statistical analysis methods will be elaborated in the SAP.

11. Clinical Trial Management

11.1 Statement

This clinical study will be conducted according to the standard operating procedures of the sponsor and CRO. The procedures are established aiming at guaranteeing that this trial can be conducted in accordance with the requirements of *Declaration of Helsinki*, E6 Guidelines for Good Clinical Practice issued by ICH, GCP issued by NMPA and drug clinical trial regulations.

When signing the protocol, the investigator will agree to conduct the study in strict accordance with the protocol, clinical trial specifications, and relevant laws and regulations, and keep all the information provided by the sponsor in accordance with confidentiality requirements.

11.2 Ethics

This study is designed and prepared on the basis of *Declaration of Helsinki* of World Medical Association after the consideration of rights and welfare of patients. The principal investigators or investigators of the clinical trial are required to explain the purposes and all potential possibilities of this trial to subjects. The patient who voluntarily agrees to participate in the clinical trial and signs the ICFs will be regarded as a subject of this trial.

Clinical trial investigator and site staff participating in the trial should appropriately understand and be familiar with study protocol, and prepare in advance, such as for treatment measures in case of unexpected AEs, required reports and sufficient training. Clinical investigators must comply with the *Declaration of Helsinki*, E6 issued by ICH, GCP issued by the NMPA and relevant regulations when conducting the clinical trial.

The principal investigator and study personnel participating in the study should follow the contents specified in the study protocol and scientifically maintain currently accepted technical level in conducting the trial.

In accordance with national policies and regulations, the investigator should provide trial-related documents to the Ethics Committee.

The approval of the Ethics Committee and drug regulatory authorities must be obtained before the initiation of clinical study.

Modifications to the study protocol should be submitted to the Ethics Committee for review and approval and sent to Health Authorities for record keeping according to the local requirements.

During the clinical study period, should any SAEs or unexpected AEs which are associated with clinical study safety and may affect the safety of subjects and study implementation occur, the investigators should report to the Ethics Committee according to the regulatory requirements.

The Ethics Committee should be informed of the end of study.

11.3 Source Data Verification

The investigator must properly handle all data obtained during the clinical study to ensure the rights and privacy of subjects participating in the clinical study. The investigators must allow the monitors/auditors/inspectors to review and check the required clinical study documents so as to verify the accuracy of the source data and learn about the study progress. If the source data cannot be verified, the investigators should agree to assist the monitors/auditors/inspectors in the further confirmation of data quality control.

11.4 Quality Assurance and Review

All drugs and materials used in the clinical study must be on the premise of quality control. The sponsor and its authorized personnel or related medical management agencies have the right to review the clinical study, the purpose of which is to ensure the authenticity of recorded data for the clinical study and to comply with the provisions of the clinical study protocol.

This study will be organized, performed and reported according to the study protocol as well as the standard operating procedures of the sponsor and CRO. In ICH E6, Quality Assurance (QA) is defined as "all of those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, recorded, and reported in compliance with GCP and applicable regulatory requirements". The sponsor's QA will be carried out in accordance with the regulations of the study audit plan. Section 5.19.3 (b) of ICH E6 stipulates that the audit plan and procedures for a trial audit should be guided by the importance of the trial to submission to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problems. The QA work can be outsourced to a CRO or an independent consulting agency. The investigators are required to support auditing work, attend auditing activities as required by the auditor, and allow the auditors to directly have access to source data/documents, including all medical records, study-related documents and correspondences, and the informed consent documents of this clinical trial. The clinical study subjects will be informed of such clinical study inspecting or auditing process, but the privacy and data materials of subjects will be strictly protected.

11.5 Informed Consent Form

The investigators are responsible for explaining the purposes, methods, benefits and potential risks of this clinical trial, other optional treatment methods, rights and obligations to each subject meeting the requirements of the *Declaration of Helsinki*. The subjects should be informed that they have rights to withdraw from this trial at any time while their personnel interests will not be impaired. The informed consent form signed by the subjects must be obtained before the initiation of any clinical trial-related procedures.

The verbal explanation must be given when the written informed consent form is provided for subjects. The informed consent form must be dated and signed by each subject or his/her legal guardian or impartial witness. The signed informed consent form in duplicate (including information page) is kept by subjects. The other signed informed consent form will be retained

and preserved as study files at the study sites.

Before the initiation of any study-related procedures, the informed consent form must be approved and signed by the subject or his/her legal guardian or impartial witness. Before obtaining informed consent, the investigator or his/her designated personnel should provide the subject with sufficient time and opportunity to ask about details of the trial and decide whether to participate or not. The process of the informed consent should be documented in the disease course records at the day of screening visit or medical records.

The investigator should be responsible for the process of informed consent. If any information related to subject's willingness to continue to participate in this study is obtained during the study period, the informed consent form must be updated and provided for subjects to confirm whether the subjects are willing to continue this study. The amended informed consent form can be provided to subjects after it is approved by the Ethics Committee.

After signing the informed consent form, the subjects must also agree that the sponsor, drug approval regulatory authorities, auditors and/or the sponsor-authorized clinical trial monitors check the available source data related to clinical study. Moreover, the reviewer must follow confidential statement.

11.6 Revision to the Clinical Protocol

After this protocol has been approved by the Ethics Committee, in case any amendment has been made to the protocol during the conduct of the study, the amendment can be implemented only after being submitted to the Ethics Committee and the approval is obtained.

Any changes to the protocol are required to be made in a written form, regardless of major or non-major protocol amendments. Substantive protocol modifications which may definitely affect the safety of subjects, study scope or scientific quality of this study should be approved by the Ethics Committee of all study sites. To protect the safety of all subjects in the study, the above requirements shall not preclude the investigator or the sponsor from taking any emergency action. If the investigators consider it necessary to perform immediate protocol change for safety consideration, they must immediately notify the institutions designated by the sponsor and inform the Ethics Committee of study sites according to the policies stipulated by the Ethics Committee who approves this study, local regulations and policies. Any changes which affect study administration only do not require substantive protocol modifications or approval from the Ethics Committee, however, these changes must be reported to the Ethics Committee. Under these conditions, the sponsor will send an authentication letter to the Ethics Committee to carefully specify these changes.

11.7 Protocol Deviations

The investigator should conduct this clinical trial according to the clinical study protocol approved by the Ethics Committee and GCP regulations. The protocol is established to make the investigator follow regulations in ICH E6 Section 4. During the trial, the investigator should

avoid protocol deviation, except emergency action taken to avoid direct harm to subjects. In case of other unexpected situation requiring deviation from protocol-specified procedures, the investigator should discuss with the medical monitor (and Ethics Committee when necessary) to determine appropriate measures.

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

11.8 Case Report Form

The CRO database programmer will establish eCRFs in the EDC system on which different subjects will be identified only by appropriate identification codes (e.g., site number and subject number) and initials. eCRF is used to record the clinical research data of subjects and is an integral part of the study and related study reports, so the entry must be accurate and complete. Data entry into eCRF will be made by the investigator or a person authorized by the investigator (should be specified in study authorization form) in EDC system. All data entries must be ensured to be completed and stored. The investigator must provide an electronic signature to declare that all information in the eCRF is true and correct.

In clinical study, eCRF should be completed as soon as possible after each visit to record the condition of subjects.

The medical records and other records related to disease progression of subjects during the study period will be stored by the investigator. These records should contain the following contents: original or copy of laboratory data and other medical test results (e.g., ECG). These materials must be stored at site with subjects' medical records.

11.9 Monitoring

Monitoring will be conducted by the sponsor or the CRO entrusted by the sponsor.

During the study, the monitors should routinely perform on-site monitoring at each study site. At each monitoring, visit date will be documented at site visit records of the study sites. Whether or not to perform site monitoring will be decided by the sponsor depending on the study quality.

Study monitoring activities of monitors include:

- Perform study initiation visit to the study site, collect and distribute necessary documents before study; provide guidance and description of the protocol, study procedure and expectation to investigators and site staff; obtain investigators' guarantee of conducting the trial in compliance with study requirements and the GCP and introduce study materials to investigators and corresponding study staff.
- Monitoring visit: According to the requirements of GCP, CRAs taking part in the current

study should completely understand affairs of confidentiality and compare the data in the eCRF with those in the hospital or clinical record (original materials). Before starting the study, the CRAs should discuss with the investigator specific items required for the original materials, confirm the nature and preservation address of all original materials to ensure the sponsor and the investigator is aware of the source of the original materials for finishing the eCRF and the CRA's right of inspection and verification authorized by the sponsor; all observations and findings during monitoring should be verified. If the electronic records are stored at study institutions, the verification methods must be discussed with the study personnel.

Source documents must be available to confirm:

- The identity of subject, whether the subjects are eligible and participate in the study;
- Appropriate informed consent procedure;
- Visit date;
- Records of safety and efficacy parameters;
- Sufficient reports and visits of AEs;
- Treatment with concomitant medications;
- Records of reception/dispensation/return of drugs;
- Administration information of the study drug;
- Subjects' completion of treatment, termination of treatment or withdrawal from the study and appropriate reasons;
- That the data are authentic, accurate and complete;
- That the safety and rights of subjects are protected;
- That the investigator's implementation complies with the current approved protocol, GCP and all relevant regulatory requirements.

The objectives to be achieved by the monitoring include:

- Check and evaluate the study progress;
- Reviewing the collected study data;
- Implement source file verification process;
- Identify any problems and develop solutions.

During the study, the monitor should only have direct access to all relevant documents with the consent of the investigator, and the investigator should ensure that he/she and relevant site staff meet with the monitor regularly to discuss the findings and any relevant problems during the visit.

11.10 Subject Privacy

The study staff must ensure that the privacy of subjects in clinical trials is protected. In all documents and files submitted to sponsor, the clinical trial subjects can only be identified by clinical trial screening/randomization number and initials, while the full name of a subject is never indicated. The investigator must store the private information, e.g., name and address, of the subjects in the clinical trial in a strictly confidential manner, and may not submit it to the sponsor.

12. Paper Publications

The study results are proprietary to the sponsor. The investigator should guarantee that he/she will not publish on journals or magazines or release on academic or commercial conferences about any content related to the study and/or study results without the written permission from the sponsor. The sponsor has the right of final decision about the manuscript and publication. At the same time, the investigator should understand that the sponsor will not refuse the publication without any reason after being communicated.

In order to prevent from unconscious leakage of confidential information or unprotected inventions, the investigator must inform the sponsor in advance to discuss or review together about publications planned to be published or releases in other forms (the forms of publication/release include but are not limited to journal articles, posters, guest lectures). Prior to publication, the sponsor may request that the investigator delete any confidential information that has not been published before.

13. Material Retention

13.1 Source Data and Source Files

In this trial, the source data includes clinical findings, observations, and records of other related activities required to reconstruct and evaluate the clinical trial. The original data is contained in the source files.

The source files involved in the clinical study are original records, documents and data (such as hospital medical records, medical images, laboratory records, memos, subject diaries or assessment forms, drug distribution records, data automatically recorded by instruments, microfilms, photographic plates, X-rays, subject files, clinical trial-related documents and records kept by pharmacies, laboratories, and medical technology departments, including certified copies, etc.). Source files must be preserved to support the information provided in the eCRF.

13.2 Materials Retention of Study Sites

13.2.1 Materials related to the Ethics Committee

The personnel in the study site who are responsible for storage of materials must retain the conference minutes and synopsis of the Ethics Committee until 5 years after study termination or completion. If the sponsor wishes to retain the materials for a longer period of time, the retention time and methods will be discussed and decided by both parties. If the study site makes any changes in document retention, personnel or investigator responsible for document retention should contact the sponsor.

13.2.2 Materials related to the trial implementation

The personnel in charge of materials preservation in the study site must keep the following files until 5 years after the investigational drug is approved for marketing. If the sponsor wishes to retain the materials for a longer period of time, the retention time and methods will be discussed and decided by both parties. If the study site makes any changes in document retention, personnel or investigator responsible for document retention should contact the sponsor.

- Original materials;
- The original or copy of the trial contract and informed consent form, and other GCP-related materials provided by the staff of the study site;
- Trial protocol, GCP-related materials obtained from the Ethics Committee, or other GCP-related materials obtained;
- Records of management of the study drug and other records related to trial implementation.

13.3 Material Retention of the Sponsor

The sponsor will keep the following materials (including files and data) until 5 years after the investigational drug is approved for marketing. A longer retention period may be required

according to relevant regulations. It is the responsibility of the sponsor to inform the investigator/study site of when it is no longer necessary to further retain such data.

- The original or copy of the trial protocol, trial contract and study report, or GCP-related materials provided by the sponsor;
- Case report form, GCP-related notices, or GCP-related materials obtained from the investigator;
- Records associated with monitoring and audits, or other relevant operation records;
- Data obtained in the trial;
- Relevant records specified in GCP.

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15. Appendices

Appendix 1: COVID-19 Symptoms Scoring Scale

Subjects should complete the COVID-19-related Symptom Scoring Scale every day, including 11 target symptoms and other COVID-19 symptoms (see Attached Table 1 and Attached Table 2). The symptom scoring on D1 should be completed prior to the first dose, and the COVID-19-related Symptom Scoring Scale should be completed at approximately the same time each day thereafter. The subject should score according to the worst severity of each symptom in the past 24 hours. Subjects may fill in the score scale under the guidance or assistance of the investigator. If it is a telemedicine visit, the investigator is to instruct the subject to complete it via telephone.

Sustained recovery of clinical symptoms is defined as with the score of 0 for all COVID-19-related target symptoms (see Attached Table 1) for 2 consecutive days.

Time to sustained recovery of clinical symptoms is defined as the number of days from the first dose after randomization to the first day when all COVID-19-related target symptoms (see Attached Table 1) are scored 0 for 2 consecutive days.

Sustained alleviation of clinical symptoms is defined as with the score of ≤ 1 for all COVID-19-related target symptoms (see Attached Table 1) for 2 consecutive days.

Time to sustained alleviation of clinical symptoms is defined as the number of days from the first dose after randomization to the first day when all COVID-19-related target symptoms (see Attached Table 1) are scored ≤ 1 for 2 consecutive days.

Attached Table 1 Target COVID-19 Symptoms Scoring Scale

Target symptom	No (0 scores)	Mild (1 score)	Moderate (2 scores)	Severe (3 scores)
Fever*	No	37.3-38℃	38.1-38.9℃	⩾39℃
Cough	No	Occasional cough	Intermittent cough	Frequent cough, with influence in sleeping at night
Congestion or runny nose	No	Mild congestion or runny nose	Marked congestion or runny nose	Severe congestion or runny nose, resulting in shortness of breath
Sore throat or dry throat	No	Mild sore throat or dry throat	Marked pain pharynx, or marked dry throat requiring increased water intake	Severe pain pharynx, affecting swallowing; or severe dry throat, which cannot be relieved by drinking water
Shortness of breath or difficulty breathing	No	Occasional shortness of breath or difficulty breathing	Marked polypnoea or dyspnoea	Severe shortness of breath or difficulty breathing, requiring rest to relieve
Headache	No	Occasional mild	Marked headache	Severe headache requiring

		headache	with frequency increased	rest
Muscle or body aches	No	Mild muscle or body aches	Marked muscle or body aches	Severe aches, with influence on daily living
Diarrhoea (within the past 24 h)	No	Diarrhoea for once or twice	Diarrhoea for three or four times	Diarrhoea for five times and more
Chills	No	Mild chills	Marked chills	Severe chills requiring warming up
Nausea	No	Transient nausea with food intake generally normal	Intermittent nausea leading to reduced food intake	Persistent nausea leading to substantially reduced food intake
Vomiting (within the past 24 hours)	No	Vomiting for once or twice	Vomiting for three or four times	Vomiting for five times and more

*Body temperature is measured under the armpit.

Attached Table 2 Other COVID-19 Symptoms

Symptom	No (0 scores)	Mild (1 score)	Moderate (2 scores)	Severe (3 scores)
Asthenia or fatigue	No	Slight asthenia or fatigue	Marked asthenia or fatigue, requiring rest	Severe asthenia or fatigue, with increase in rest or bed-rest time
Decrease or loss of taste (within the last 24 hours)	No	With taste worse than usual	Total loss of taste	
Decrease or loss of smell (within the last 24 hours)	No	With smell worse than usual	Total loss of smell	

Appendix 2: WHO Clinical Progression Scale

The investigator should complete the WHO Clinical Progression Scale after inquiring the subject. The scale scoring on D1 should be completed by the investigator prior to the first dose, and the WHO Clinical Progress Scale should be completed at approximately the same time for each visit thereafter. The investigator should score according to the worst severity of the subject in the past 24 hours. In case of telemedicine visit, the investigator will call the subject every visit to inquire about the subject and complete the WHO Clinical Progression Scale in a timely manner.

Attached Table 3 WHO Clinical Progression Scale

Patient status	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Non-hospitalized, mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy*	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $PO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7 8
	Mechanical ventilation $PO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	9
	Mechanical ventilation $PO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	
Death	Death	10

Abbreviation: ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; NIV = noninvasive ventilation; PO_2 = partial pressure of oxygen; SpO_2 = peripheral oxygen saturation

*If a patient is hospitalized for other reasons such as convenience of observation and management, an inpatient status cannot be recorded. Inpatient status can only be recorded until there is a disease progression or the severity of the condition meets the hospitalization criteria as assessed by the investigator.

Appendix 3: Definition of Women of Childbearing Potential and Contraceptive Requirements

Definition of Women of Childbearing Potential

Women of non-childbearing potential are defined as postmenopausal women and premenopausal women who have undergone sterilization. Postmenopausal is defined as continuous menopause ≥ 12 months without alternative medical measures. Subjects with uncertain menopausal status can be tested for follicle stimulating hormone (FSH). If FSH is > 40 mlU/mL, menopause can be confirmed. Sterilization includes bilateral tubal ligation or bilateral oophorectomy or hysterectomy.

Women of childbearing potential are defined as women who have not undergone sterilization and are able to become pregnant anatomically and physiologically after menarche and before menopause.

Female subjects of childbearing potential and male subjects without prior vasectomy must take effective contraceptive measures thoughout the whole study period from the signing of the ICF and for 28 days after the end of the study, including one of the following operations:

- Total abstinence. Periodic abstinence methods (such as calendar method, ovulation method, symptom-body temperature method, post-ovulation method) are not allowed.
- One of the contraceptive methods with a failure rate of < 1%:
  - Intra-uterine contraceptive device or intra-uterine hormone release system with an annual failure rate of < 1%;
  - Males undergo vasoligation;
  - Double barrier method: Condoms and/or occlusion caps (diaphragm or cervical cap/dome cap), spermicide (foam/gel/film/cream/suppository) barrier method should be used as supplementary measures.

Appendix 4: Examples of Representative Drugs with Possible Drug Interaction Risks

Drugs that may have drug interaction risks include: any drugs or substances that are highly dependent on CYP3A4, CYP2B6, CYP1A2, MDR1 or OATP1B3 for clearance; potent CYP3A4 or MDR1 inducers.

Drugs highly dependent on CYP3A4 for clearance	α-1 adrenergic receptor antagonists: Alfuzosin Antiangina drug: Ranolazine Antiarrhythmic drugs: Amiodarone, dronedarone, flucamide, propafenone, quinidine Anti-gout: Colchicine Antipsychotic drugs: Flurasidone, pyrazine Agents for benign prostatic hyperplasia: Silactose Cardiovascular drugs: Eplerenone, ivabradine Ergot derivatives: Dihydroergotamine, ergotamine and methylergonovine HMG-CoA reductase inhibitors: Lovastatin, simvastatin Immunosuppressant: Voclosporin Microsomal triglyceride transfer protein inhibitor: Lomitadine Migraine drugs: Eletriptan, ubrogepant Mineralocorticoid receptor antagonist: Finerenone Opioid antagonist: Naloxigo PDE5 inhibitor: Sildenafil Sedative/hypnotic drugs: Triazolam, oral midazolam Serotonin receptor 1A agonists/5-hydroxytryptamine receptor 2A antagonists: Flubanserine vasopressin receptor antagonist: tolvaptan
Potent CYP3A4 inducers	Anticancer drug: Apalutamide Anticonvulsant drugs: Carbamazepine, phenobarbital, primicone, phenytoin sodium Modulating enhancers of cystic fibrosis transmembrane conductance: Lumacaftor/Ivacaftor Antifungal drug: Rifampicin Herbal products: St. John's wort (Hypericum perforatum)
Drugs or substances dependent on CYP2B6 for clearance	Anesthetics: Ketamine, lidocaine, propofol Antiarrhythmic drug: Mexiletine Anticoagulant drug: Coumarin Anticonvulsive drug: Mephenytoin Antidepressive drug: Amfebutamone Antiepileptic drug: Meflurbarbital, valproic acid Anti-inflammatory drugs: Aminopyrine, antipyrine, tazofelone Antimalarial drugs: Artemisinin, artemether Antiretroviral drugs: Efavirenz, nevirapine Chemotherapeutic drugs: Cyclophosphamide, ifosfamide, tamoxifen Monoamine oxidase inhibitors: Selegiline Opioids: Methadone, meperidine Psychotropic drugs: Clonazepam, diazepam, temazepam Steroid: Testosterone

Drugs or substances dependent on CYP1A2 for clearance	Caffeine, clozapine, theophylline, propranolol, heterocyclic amines, aflatoxin
Drugs or substances dependent on MDR1 for clearance	Analgesics: Asimadoline, morphine Antibiotics: Erythromycin, valamamycin, gramicidin, rifampicin, garenoxacin Antitumor drugs: Vincristine, paclitaxel, anthracycline, podophyllotoxin, etc. Antidepressive drugs: Venlafaxine, paroxetine Antidiarrheal drug: Loperamide Antiemetics: Domperidone ondansetron Antiepileptic drugs: Carbamazepine, phenobarbital, phenytoin, lamotrigine, felbamate Antifungal drug: Itraconazole Anti-gout: Colchicine Antiarrhythmic drugs: Talinolol, verapamil, digoxin Corticosteroids: Dexamethasone, hydrocortisone, corticosterone, triamcinolone acetonide Aldosterone Diagnostic dyes: Rhodamine 123, Hearst 33342 HIV protease inhibitors: Saquinavir, ritonavir, nelfinavir, indinavir, lopinavir, amprenavir Histamine receptor blockers: Fexofenadine, cimetidine Immunosuppressants: Cyclosporine A, tacrolimus Proton pump inhibitors: Omeprazole, lansoprazole, pantoprazole Insecticides: Ivermectin, abamectin Statins: Lovastatin Natural product ingredients: Flavone, coumarin, berberine
Drugs or substances dependent on OATP1B3 for clearance	Bosentan, digoxin, enalapril, erythromycin, fexofenadine, fluvastatin, pitavastatin, pravastatin, rosuvastatin, rifampicin, olmesartan, telmisartan, atrasentan, valsartan, imatinib, methotrexate, paclitaxel, docetaxel, CCK-8, cefradine, cefazolin, cefmetazole, cefditoren, cefalexin, nafcillin
MDR1 inducers	Aspirin, carbamazepine, topiramate, ceramide-1-phosphate, stanniocalcin 2, 1α, 25-dihydroxyvitamin D3, aconitine, benzoyl aconitine, aconine, rosmarinic acid, artificial bezoar, rhynchophylline

Appendix 5: Calculation Formula

QTcF calculation formula

$QTcF = QT / RR^{0.33}$

Appendix 6: Clinical Laboratory Tests

Item	Content
Hematology	White blood cell count, neutrophil percentage, lymphocyte percentage, neutrophil count, lymphocyte count, red blood cell count, hemoglobin, platelet count
Urinalysis	Urine glucose, urine occult blood, urine protein, urine red blood cell count, urine white blood cell count
Blood biochemistry	**Liver function:** Lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, albumin, total bilirubin, direct bilirubin, indirect bilirubin; **Renal function:** Urea nitrogen or urea, creatinine; **Electrolytes:** Sodium, potassium, chloride, calcium; **Lipid:** Total cholesterol, triglycerides; Blood glucose
Urine pregnancy test	Human chorionic gonadotropin
Other tests	SARS-CoV-2 IgM/IgG, CD3/CD4/CD8, procalcitonin, erythrocyte sedimentation rate, CRP and IL-6

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

Appendix 7: Clinical Classification and Severe/Critical High-risk Populations in *Diagnosis and Treatment Protocol for COVID-19 (Trial Version 10)*

(I) Mild.

Upper respiratory tract infection is the main manifestation, such as dry throat, sore throat, cough, and fever, etc.

(II) Moderate.

Sustained high fever > 3 days or (and) cough, tachypnea, etc., but respiratory rate (RR) < 30 bpm, oxygen saturation > 93% when perform inspiration at resting. The characteristic COVID-19 manifestation is shown by imaging.

(III) Severe.

Adults who meet any of the following, with the symptom not explained for reasons other than COVID-19:

1. Tachypnea, RR ≥ 30 breaths/min;
2. Oxygen saturation ≤ 93% when perform inspiration at resting;
3. Arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg (1 mmHg = 0.133 kPa); in high-altitude areas (at an altitude of over 1,000 meters above sea level), PaO_2/FiO_2 shall be corrected by the following formula: PaO_2/FiO_2 × [760/atmospheric pressure (mmHg)].
4. Clinical symptoms progressively worsened, and lung imaging that shows obvious lesion progression within 24-48 hours ≥ 50%.

(IV) Critical.

Subjects meeting any of the following:

1. Respiratory failure and requiring mechanical ventilation;
2. Shock;
3. Combined with other organ failures that requires ICU care.

Severe/critical high-risk population:

(I) Age > 65 years, especially those who have not received full-course vaccination against COVID-19;

(II) Patients with underly diseases such as cardiovascular and cerebrovascular diseases (including hypertension), chronic pulmonary diseases, diabetes mellitus, chronic hepatic or renal disorders, and malignancies, and patients on maintenance dialysis;

(III) Patients with immunodeficiency disease (e.g., patients infected with HIV, long-term use of corticosteroids or other immunosuppressive agents leading to decreased immune function);

(IV) Obesity (body mass index ≥ 30);

(V) Females in late trimester of pregnancy and perinatal period;

(VI) Heavy smoker.

Appendix 8: Medication Guide for Symptom alleviation During the Study

Recovery of COVID-19-related symptoms is the primary endpoint of this study. If the relevant symptoms in the subject are mild, no intervention is required unless necessary, and it is recommended to observe the symptoms for 1-2 days first; if the subject remains intolerable and strongly requests medication, drug intervention can be considered as described in the table below, but should be avoided whenever possible.

	Name of concomitant medication	**Indication**	**Advice and reason for use**
Fever	**Acetaminophen**	Fever	**Not to be used unless necessary:** sustained-release preparations should not be used, instead common preparations are recommended; do not use whenever possible in case of mild fever; use as symptomatic treatment in case of severe symptoms of fever. Measure temperature and evaluate for COVID-19 symptoms before or > 4 hours after dosing.
	Ibuprofen suspension drops/ Other preparations such as sustained-release capsules		Prohibited medication
	Indomethacin		Prohibited medication
	All diclofenac sodium preparations		Prohibited medication
	Loxoprofen Sodium Tablets		Prohibited medication
	Aspirin Effervescent Tablets		Prohibited medication
	Analgin Tablets		Prohibited medication
	Antipyriine and Caffeine Citrate Tablets		Prohibited medication
	Compound Aminopyrine Phenacetin Tablets		Prohibited medication
Compound cold drugs	**Compound cold drugs (wan'an: amantadine; mei: dextromethorphan; anfen: acetaminophen; weima: pseudoephedrine; min: antiallergic: chlorpheniramine; ka: caffeine; huang: artificial bezoar)**	Cold-related symptoms	Prohibited medication
Nose	**Ephedrine Hydrichloride and Nitrofurazone Nasal Drops**	Nasal congestion	Prohibited medication
Cough-relievin	**Common cough suppressants**	Cough, expectoration	**Do not use unless necessary; the specific suggestions are as follows:**

	Name of concomitant medication	Indication	Advice and reason for use
g and phlegm - reducing			1. The order of recommendation for cough medications: throat lozenge > King-to Nin Jiom, strong loquat dew, lung-ventilating> Juhong, Feilike, Suhuang > Ambroxol, Licorice Tablets, Compound Methoxyphenamine 2. The recommendation is made in ascending order of cough-relieving effect. Select medication according to the type and severity of cough. It is recommended to observe the symptoms for 1-2 days first; if the subject remains intolerable and strongly requests medication, consider giving drug intervention, but avoid using the last 3 drugs whenever possible. Reason: As symptoms recovery is the primary endpoint of this study, and cough is one of the symptoms to be observed, intervention is not to be given unless necessary
	Cough drugs with central antitussive ingredients like dextromethorphan or codeine, etc.	Expectoration	Prohibited medication
Anti-allergic	**Cetirizine (drops + tablets), Chlorpheniramine Tablets, Loratadine**	Allergic rhinitis, bronchitis, cough	Oral medication is prohibited; topical ointment can be used as appropriate
Digestive system	**Gastrointestinal excitomotors such as Mosapride Tablets and Domperidone Suspension**	Gastrointestinal excitomotors	Prohibited medication
	Lactulose Oral Solution Combined Bifidobacterium, Lactobacillus, Enterococcus and Bacillus Cereus Tablets, Live	Diarrhea, constipation	**Can be used, but attention should be paid to the dosage. Reason:** When the dosage is higher than the recommended therapeutic dosage, abdominal pain and diarrhea may occur, so attention should be paid to the dosage; it may interfere with COVID-19 symptoms scoring, so care should be taken to distinguish from the gastrointestinal symptoms caused by COVID-19.
	Compound Digestive	Dyspepsia	**Do not use unless necessary. Reason:**

	Name of concomitant medication	Indication	Advice and reason for use
	Enzyme II Capsules		Compound Digestive Enzyme II Capsules may cause mild diarrhea and mild AST elevation, which can recover without treatment. When assessing the relationship to the study drug, care should be taken to distinguish these symptoms.
	Montmorillonite Powder	Diarrhea	Prohibited
Others	**Glucocorticoids**	Anti-inflammatory	Prohibited medication. Topical ointments such as methylprednisolone, dexamethasone, and hydrocortisone may be used as appropriate.
	Lianhua Qingwen Capsules	To relieve various symptoms	Prohibited medication
	Chinese patent medicines and Chinese herbal medicines	Antiviral and symptoms-relieving	Prohibited. Reasons: [1] Many traditional Chinese medicines, e.g., Qingfei Paidu Decoction/Granules, have inhibitory effect on CYP3A4 activity, as their ingredients may include CYP3A4 inhibitors, which may increase the incidence of adverse drug reactions; [2] They may relieve various symptoms, thus affecting the evaluation of the primary endpoint. 2. Chinese herbal medicines that evidently may cause abnormal liver function are prohibited; 3. Chinese herbal medicines that are highly dependent on CYP3A4 clearance are prohibited; 4. Chinese herbal medicines that are potent CYP3A4 inducers, e.g., hypericum perforatum, are prohibited.

Note: Drugs not listed in this appendix should not be assumed to be permitted. The investigator will review any concomitant medications and confirm whether they can be used.