**Appendix 2 Clinical Study Protocol**

**Preventive Efficacy of Lianhua Qingwen Capsules on Close Contacts of Seasonal Influenza in a Clustered Environment: A Multicenter, Randomized, Double-blind, Placebo-controlled Study（Life Force）**

|  |  |
| --- | --- |
| **Protocol No.:** | LHQW-CTP |
| **Coordinating PI:** | Dr. Zhong Nanshan  First Affiliated Hospital of Guangzhou Medical University |
| **Sponsor:** | First Affiliated Hospital of Guangzhou Medical University |
| **Protocol Version No.:** | 1.1 |
| **Protocol Version Date:** | July 15, 2023 |

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| --- |
| **Confidentiality Statement**  All the information contained in this protocol is owned by the First Affiliated Hospital of Guangzhou Medical University and is only reviewed by investigators, co-investigators, the Ethics Committee, the Contract Research Organization, supervision and regulation departments and other relevant medical institutions. It is strictly forbidden to use and copy the content of this study protocol or to inform third parties unrelated to this study of any information without consent, except to provide the subjects with the necessary explanation for obtaining informed consent. |
| **Declaration of Conformity**  This study will be implemented in accordance with China’s *Drug Administration Law*, *Provisions for Drug Registration* and *Good Clinical Trial Practice* (GCP). All the personnel involved in the implementation of this study must have been trained in GCP.  The study protocol, the informed consent forms (ICF), recruitment materials and all the other relevant materials will be submitted to the Institutional Review Board (IRB) for review and approval prior to implementation. All the changes and revisions are subject to review and approval by the IRB before implementation; it should also be determined whether subjects who have signed on the previously approved version of the ICFs need to sign the new version of ICFs again. |

**Protocol Signature Page**

**Statement of Investigator**

I will conscientiously perform my duties as an investigator in accordance with the relevant regulations of GCP.

I have read about this protocol, and this study will be implemented in accordance with the moral, ethical and scientific principles required by the *Declaration of Helsinki* and China’s GCP. I agree to carry out this clinical trial in accordance with the design and regulations of this protocol.

I will be responsible for making clinically relevant medical decisions to ensure that subjects are treated promptly and appropriately when adverse reactions (AR) occur during the trial, and I am aware of the requirements for proper reporting of serious adverse events (SAE), which I will record and report as required.

I guarantee that the data will be recorded in the case report form in a truthful, accurate, complete, timely and lawful manner. I will accept the audit and inspection by clinical research associates (CRA) or auditors dispatched by the Sponsor and by the drug regulatory authorities to ensure the quality of clinical trials.

I agree with the publication of the trial results.

I will provide and submit a CV prior to the start of the trial to the Ethics Committee and possibly to the drug regulatory authorities for review.

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| --- | --- |
| **Signature** | **Date** |
| First Affiliated Hospital of Guangzhou Medical University | (MM/DD/YYYY) |

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| **Signature** | **Date** |
| <Name of Principal Investigator>  <Name of Research Unit> | (MM/DD/YYYY) |

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# 1. Synopsis of Protocol

## 1.1 Introduction

|  |  |
| --- | --- |
| **Protocol No.** | LHQW-CTP |
| **Investigational Drug** | Lianhua Qingwen Capsules |
| **Registered Title** | Preventive Efficacy of Lianhua Qingwen Capsules on Close Contacts of Seasonal Influenza in a Clustered Environment: A Multicenter, Randomized, Double-blind, Placebo-controlled Study |
| **Scientific Title** | A Randomized, Double-blind, Multi-center Clinical Trial for Evaluating Effectiveness, Safety and Economy of Preventive Efficacy of Lianhua Qingwen Capsules on Close Contacts of Seasonal Influenza in a Clustered Environment |
| **Type of Clinical Trial** | IIT |
| **Summary of Clinical Trial** | In this study, a randomized, double-blind, multicenter design method was used to evaluate the effectiveness and safety of Lianhua Qingwen Capsules in a clustered environment on close contacts of seasonal influenza, which will provide a basis for clinical use. The treatment cycle of this study is expected to be 5 days, and 1,884 close contact subjects are planned to be enrolled. All cases are randomly assigned to the test group or the control group as index cases, and the subjects need to receive 3 visits during the treatment respectively on the 3rd, 5th and 9th days after taking the drug for corresponding examinations. Symptom scoring will be performed every night during the trial. |
| **Coordinating PI** | Dr. Zhong Nanshan |
| **Test Facilities** | Responsible facility: 01, First Affiliated Hospital of Guangzhou Medical University  Participating facilities: To be determined  *Note: During the clinical trial, the participating facilities may adjusted as actually required, which will not be amended in the protocol then (unless there are other amendments at the same time), but the new participating facilities should complete the protocol signature page.*  *The study sites are numbered by acronym and sorted in alphabetical order. If a new participating facility replaces the original one, the same number of the original participating facility should be kept for it; If the new participating facility is an added one, its number will be added in chronological order.* |
| **Study Objective** | To evaluate the effectiveness, safety and economy of preventive efficacy of Lianhua Qingwen Capsules on close contacts of seasonal influenza in a clustered environment. |
| **Study Population** | This study is expected to include 1,884 close contact subjects, and the target population is the close contacts of seasonal influenza patients, who are aged between 18 and 70 of any gender from any geographical region. |
| **Inclusion and Exclusion Criteria** | **Inclusion criteria for index cases:**  (1) Gender and age are not limited;  (2) At least two of the following flu-like symptoms appear: Fever, cough, nasal congestion, sore throat, headache, runny nose and muscle or joint pain, and the symptom score is ≥1;  (3) The flu-like symptoms first occur within 48 hours;  (4) Patients who are rapidly tested positive for influenza and meet the clinical diagnosis criteria of influenza;  (5) In addition to the index cases, there are 2 or more adult close contacts who meet the inclusion criteria and do not meet the exclusion criteria in the clustered units (i.e. the co-living environments, including the same families, school dormitories, factory dormitories and shared units, etc.);  (6) Volunteers who are willing to participate in this study and sign a written ICF.  **Exclusion criteria for index cases:**  (1) The result of COVID-19 antigen test is positive;  (2) The close contacts in the clustered units who participated in this study but are tested positive for COVID-19;  (3) Severe and critical patients who require hospitalization;  (4) Patients with other serious clinical conditions who require hospitalization or monitoring;  (5) Other patients considered by the investigator to be inappropriate to participate in this study.  **Inclusion criteria for clustered close contacts:**  (1) The index cases in the same clustered units who meet the inclusion criteria and does not meet the exclusion criteria;  (2) 18 ≤ age ≤ 70;  (3) The result of rapid influenza virus antigen test is negative;  (4) No flu-like symptoms occur within 1 week before randomization (the total score of flu-like symptoms is 0);  (5) During 9 days after randomization, persons who are expected to live with the index cases for at least 7 days and be able to participate in visits as planned;  (6) Volunteers who are willing to participate in this study and sign a written ICF.  **Exclusion criteria for clustered close contacts:**  (1) The result of rapid COVID-19 antigen test is positive;  (2) Pregnant perinatal and nursing women;  (3) Patients combined with serious diseases of major organs or systems such as heart, brain, respiratory system, circulatory system, endocrine system, immune system, and hematopoietic system (such as congestive cardiac failure, with severity levels of III to IV by NYHA classification; significant arrhythmias or abnormal heart valves that cause hemodynamic impairment; history of unstable angina or myocardial infarction within the past 6 months; malignant tumors in the non-radiotherapy or non-chemotherapy stable period; advanced stage of pulmonary tuberculosis; severe hypertension; diabetic complications such as diabetic ketoacidosis; immunodeficiency diseases such as HIV that have not achieved immune function reconstruction; autoimmune diseases such as systemic lupus erythematosus);  (4) ALT > 5 ULN, AST > 5 ULN or SCr >1.5 ULN in the screening results;  (5) Persons who have taken Lianhua Qingwen preparation or any drugs with antiviral effect within 7 days. (Such as: Jinhua Qinggan, Qingkailing, Shufengjiedu, Yinqiaojiedu, Sangjuganmao, Banlangen, Yinhuang, oseltamivir, zanamivir and peramivir in any dosage form);  (6) Persons who have been vaccinated against influenza within 6 months;  (7) Persons who are allergic to the investigational drug;  (8) Patients who have participated in other drug clinical trials within 1 month prior to the screening test;  (9) Other patients considered by the investigator to be inappropriate to participate in this study. |
| **Efficacy Endpoints** | **Primary efficacy endpoints:**  (1) The secondary infection risk (SIR) of influenza to the close contacts taking Lianhua Qingwen capsules or the placebo within 9 days (±1 day) after randomization, i.e. the proportion of close contacts of secondary transmission of influenza including symptomatic and asymptomatic cases.  Definition of secondary transmission of influenza: The secondary transmission is inferred to be confirmed by positive RT-PCR testing result for influenza and the consistency between the virus subtypes of any nasal swab or throat swab samples collected during the study period and the index cases.  **Secondary efficacy endpoints:**  (1) The proportions of infected clustered units in all clustered units on Days 3, 5 and 9 (±1) after randomization.  Definition of infected clustered unit: An infected clustered unit is defined by positive PCR test result of any close contact participating in this study in that clustered Unit.  (2) The proportions of all the closed contacts with positive PCR test results (sum of symptomatic and asymptomatic cases) on Days 3, 5, and 9 (±1) after randomization;  (3) The proportions of all the closed contacts with positive PCR test results (symptomatic cases) on Days 3, 5, and 9 (±1) after randomization. The “symptomatic case” is defined by the presence of at least one influenza-like symptom with a flu symptom score of ≥ 1;  (4) Comparison of the mean scores of influenza-like symptoms that first occur to secondary transmission cases;  (5) The proportion of secondary transmission cases who require taking other drugs for influenza.  **Subgroup analysis:**  (1) The preventive efficacy of Lianhua Qingwen Capsules in different virus subtypes;  (2) By considering whether the index cases take antiviral drugs as a stratification factor, analyze the preventive efficacy of Lianhua Qingwen Capsules on close contacts;  **Safety indicators:**  (1) Vital signs (body temperature, heart rate, breathing, blood pressure)  (2) Physical examination  (3) Urine pregnancy test: Female subjects of childbearing age with childbearing potential are tested once during the screening period  (4) Laboratory tests  ① Blood routine examination - red blood cells (RBC), white blood cells (WBC), neutrophil count, lymphocyte count, platelet count (PLT), hemoglobin (HGB)  ② Routine urine test - urine protein (PRO), urine glucose (GLU), urine ketone body (KET), urine red blood cells (URBC), urine white blood cells (UWBC)  ③ Biochemical examination of liver and kidney functions - alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), urea/urea nitrogen (UREA/BUN), serum creatinine (SCr), albumin (ALB)  ④ Resting electrocardiogram  (5) Adverse events (AEs)/SAEs/ARs |
| **Withdrawal Criteria** | Subjects who have completed the ICFs and have been screened as eligible for enrollment (i.e. having been assigned with a random number) have the right to withdraw from the clinical trial at any time. Or, if one of the following conditions occurs during the test, the subject should be treated as a drop-out/withdrawal case:  (1) Severe comorbidities or special physiological changes occur to the subject during the trial, and the investigator believes that it is not suitable for this subject to continue to participate in the trial;  (2) The subject shows poor compliance (e.g., taking medication against the prescribed protocol; or using the contraindicated drugs in this protocol or other therapies), and the investigator believes that it is not suitable for this subject to continue to participate in the trial;  (3) The subject is unwilling to continue to participate in the trial and clearly proposes to the investigator to withdraw from the trial;  (4) The subject has not explicitly proposed to withdraw from the trial, but no longer receives medication or examination and consequently misses the follow-up visits;  (5) If an index case is screened as negative by influenza virus nucleic acid test, the clustered unit that this index case belongs to is withdrawn from the study;  (6) The close contact is screened as positive by influenza virus nucleic acid test;  (7) If an index case or a close contact is screened as positive by COVID-19 nucleic acid/antigen test, the clustered unit that this index case or close contact belongs to withdraws from the trial;  (8) Any subject who breaks blindness midway for various reasons. |
| **Elimination Criteria** | On the data review meeting before the research database is locked, the PI, the Sponsor and the relevant responsible persons of the statistical department will determine whether individual cases are eliminated. In any of the following cases, a patient should be comprehensively determined as eliminated from or included in the analysis population based on the factors such as the patient’s degree of trial completion and the reason for withdrawal, and the specific classification criteria for each analysis population will be further defined in the Statistical Analysis Plan (SAP).  (1) The participant is found not to meet the inclusion criteria or meet the exclusion criteria after inclusion.  (2) There is no record about the participant after randomization.  (3) The participant has not used the investigational drug.  (4) The effectiveness and safety cannot be determined because the case has used the contraindicated drug prescribed by the protocol.  (5) The subject shows poor compliance, and uses less than 80% or more than 120% of the prescribed drug dose during the trial.  (6) The close contact has not lived with the index cases for 7 days or more during the trial. |
| **Termination Criteria** | This study may be temporarily suspended or terminated early if there are sufficient reasonable reasons. The party that will suspend or terminate the study should immediately provide a written notice to the subjects, investigators, clinical trial institutions and drug regulatory authorities, and record the reasons for the suspension or termination of the study. Where applicable, the investigator will contact the subjects and notify any change of the scheduled visits. Conditions that may lead to the termination or suspension of the study include, but are not limited to:  (1) Any serious safety problem occurs during the trial.  (2) During the trial, the drug is found with too poor or even no efficacy, and it has no clinical value.  (3) Any major error is found in the clinical trial protocol during the trial, which makes it difficult to evaluate the drug effect; or, any important deviation is found from a good clinical protocol during its implementation, which makes it difficult to evaluate the drug effect if the trial continues.  (4) It is identified that the purpose of the study has been achieved, and the Sponsor or the investigator believes that there is no need to continue the trial.  (5) The Sponsor required discontinuance of the trial (for reasons of funding, management, etc.).  (6) The regulatory authorities request the cancellation of the trial. |
| **Interventions** | **Test group:** Lianhua Qingwen Capsules, 0.35 g/capsule, taken orally 3 times a day, 4 capsules each time;  **Control group:** Lianhua Qingwen Capsule Simulator, 0.35 g/capsule, taken orally 3 times a day, 4 capsules each time;  **Course of treatment:** Continuous medication for a total of 5 days. |
| **Visit Duration** | **Close contacts: Visit 0:** -2 - 0 day; **Visit 1:** 3 ±1 days; **Visit 2:** 5 ±1 days; **Visit 3:** 9 ±1 days; **Visit 4:** 30 ± 3 days.  Index cases: Telephone follow-up: 5 ±1 days |
| **Concomitant Medication** | The index cases receive clinical routine treatment without interventions, but the medication for treatment should be recorded in detail for analysis and reporting in the summary.  Drugs that must be continued by close contacts with underlying diseases can continue to be taken if the investigator determines that they do not violate the provisions of contraindicated drugs and do not affect the observation of the efficacy of the investigational drug; drugs or other therapies that must be continued for comorbidities must be recorded in the case report form by drug (or other therapy) name, dosage, frequency and time of usage, etc. for analysis and reporting in the summary. Contraindicated drugs Close contacts are prohibited from taking antiviral drugs throughout the trial (such as: oseltamivir, zanamivir, paramivir, favipiravir, arbidol, amantadine, rimantadine, etc.); traditional Chinese medicine or Chinese patent medicine with antiviral effect other than those specified in the protocol is also prohibited (such as: any dosage form of Jinhua Qinggan, Qingkailing, Shufengjiedu, Yinqiaojiedu, Sangjuganmao, Banlangen, Yinhuang and other preparations or antiviral oral liquids).  Before the close contacts develop flu-like symptoms, the following therapeutic drugs are contraindicated:  (1) Antibacterial and antifungal drugs;  (2) Drugs with antipyretic effect;  (3) Drugs to improve cold symptoms (antihistamines: Chlorpheniramine maleate, cetirizine, loratadine, etc.; expectorants: Ambroxol, bromohexine, acetylcysteine; drugs for contracting mucosas and blood vessels of upper respiratory tract: Pseudoephedrine hydrochloride; cough suppressants: dextromethorphan hydrobromide, codeine, etc.; or compound preparations containing the above active ingredients). Symptomatic treatment If any close contact develops flu-like symptoms, the following symptomatic treatment can be performed after the influenza symptom score form is completed the same day:  If any close contact develop fever with a body temperature above 38.5℃ continuously for more than 4 hours or above 39℃, oral non-glucocorticoid antipyretic drugs can be used. If the non-glucocorticoid antipyretic drug is used, the date and time of each dose should be recorded. If any close contact develops other flu-like symptoms, the drugs to improve cold symptoms (except traditional Chinese medicine or Chinese patent medicine) can be taken. If the drug to improve cold symptoms is used, the date and time of each dose should be recorded. |
| **Sample Size** | The primary objective of this study is to assess the risk of secondary influenza infection in close contacts of influenza who have taken Lianhua Qingwen Capsules or the placebo within 9 days (±1 day) after randomization. According to the results of previous clinical studies [28,29], the secondary transmission rate of the placebo group is estimated to be 17%, and the experimental group to be 9%; α=0.025, 1-β=0.95, and the sample allocation ratio between the two groups is 1:1; according to the calculation by PASS (2021) software, the test group and the placebo group are expected to each include 527 cases.  The enrollment in this study is based on the results of rapid influenza virus antigen test. Considering the false positive rate of index cases and the false negative rate of close contacts are estimated to be 30% in total, the sample size should be increased to 1,506 cases; plus the drop-out rate of 20%, the sample size should be further increased to 1,884 cases. Therefore, the test group and the placebo group are expected to each include 942 cases. |
| **Study Duration** | Case enrollment is expected to be completed within 24 months after the official start of the trial. |
| **Data Analysis** | **Analysis of primary efficacy endpoint**  The primary efficacy endpoint in this study is: Secondary infection risk (SIR) of influenza within 9 days (±1 day) to close contacts taking Lianhua Qingwen Capsules or the placebo, for which the comparison of difference between groups is conducted by *χ*2 test or Fisher’s exact test. The 95% confidence interval for the response rate of the two groups is estimated by the Clopper-Pearson exact method, and the 95% confidence interval for the difference of response rate between the two groups (test group - control group) is estimated by the Newcombe method.  **Analysis of secondary efficacy endpoints**  The secondary efficacy endpoints are estimated by t-test, analysis of variance, *χ*2/Fisher’s exact test or Wilcoxon rank sum test depending on the endpoint properties.  **Safety analysis**  (1) AEs and ARs: Lists are made to include all the AEs and ARs. The incidence rates of AEs (ARs) are compared between groups by *χ*2 test or the Fisher’s exact test.  (2) Abnormal changes in laboratory tests: The frequency table of normal and abnormal changes before and after treatment is listed out, and the specific list is made to include abnormal laboratory monitoring indicators changed from normal levels and seriously abnormal laboratory monitoring indicators.  (3) The vital signs of each viewpoint are described by mean, standard deviation, number of cases, minimum value and maximum value.  **Pharmacoeconomics analysis**  Based on cost-effectiveness analysis, the cost and effectiveness of two interventions are evaluated and the incremental cost-effectiveness ratio (ICER) of these two regimens is calculated to compare the economy of these two regimens.  (1) The cost consists of the direct cost and the indirect cost: The direct cost refers to medical expenses and non-medical expenses (such as transportation fee incurred by medical treatment, etc.) directly related to influenza. The indirect cost refers to work-related losses caused by influenza. The cost data is described by mean, standard deviation, median, and quartile. Depending on the endpoint properties, the comparison between groups is conducted by t-test, analysis of variance, Wilcoxon rank sum test or Kruskall-Wallis test.  (2) Effect indicators. The effect indicators include infection rate, probability of mild to moderate disease after infection, probability of severe disease, probability of hospitalization, probability of ICU use, probability of complications, and types and probability of symptoms. The comparison between groups is conducted by *χ*2 test or Fisher’s exact test. |

## 1.2 Research process

| **Day -2 to 0 of [Visit 0]** (Day 0 is the day when the close contacts are enrolled) |
| --- |
| * **Basic medical history** * ICF signing by index cases and close contacts * Rapid test of influenza virus antigen in index cases * Test of influenza virus nucleic acid in index cases * Test of COVID-19 nucleic acid in index cases and close contacts * Test of COVID-19 antigen in index cases and close contacts * Demographic data of index cases and close contacts * General clinical data of index cases and close contacts |
| * **Efficacy evaluation (for close contacts)** * Influenza symptom score * Body temperature measurement (armpit) * Rapid test of influenza virus antigen * Influenza virus nucleic acid test |
| * **Safety and other assessments (for close contacts)** * Vital signs * Physical examination * Urine pregnancy test (women of childbearing age only) * Blood routine examination * Routine urine test * Biochemical examination of liver and kidney functions * Resting electrocardiogram * AEs/SAEs/ARs |
| * **Other related work** * Recording of drug dispensing dates * Recording of concomitant medications * Dispensing of investigational drugs and daily cards * Collection of economic data, including: Assessment of patient health status (infection, severity (mild, moderate, and severe), hospitalization, ICU use, death, and complications) * Completion of eCRFs |

| **Day 3 (±1 day) of [Visit 1]** |
| --- |
| * **Efficacy evaluation (for close contacts)** * Influenza symptom score (evaluated every day during the trial) * Body temperature measurement (armpit) (measured every day during the trial) * COVID-19 nucleic acid test * COVID-19 antigen test * Influenza virus nucleic acid test |
| * **Safety and other assessments (for close contacts)** * Vital signs * Adverse events/serious adverse events/adverse reactions |
| * **Other related work** * Record the time of starting medication * Recording of concomitant medications * Recover diary cards * Issue diary cards * Collection of economic data, including: Assessment of patient health status (infection, severity (mild, moderate, and severe), hospitalization, ICU use, death, and complications) * Completion of eCRFs |

| **Day 5 (±1 day) of [Visit 2]** |
| --- |
| * **Efficacy evaluation (for close contacts)** * Influenza symptom score (evaluated every day during the trial) * Body temperature measurement (armpit) (measured every day during the trial) * COVID-19 nucleic acid test * COVID-19 antigen test * Influenza virus nucleic acid test |
| * **Safety and other assessments (for close contacts)** * Vital signs * Physical examination * Blood routine examination * Routine urine test * Biochemical examination of liver and kidney functions * Resting electrocardiogram * Adverse events/serious adverse events/adverse reactions |
| * **Other related work** * Record concomitant medication (index cases to be collected by telephone follow-up), and recover investigational drugs and diary cards * Issue diary cards * Collection of economic data, including: assessment of patient health status (infection, severity (mild, moderate, and severe), hospitalization, ICU use, death, and complications) * Completion of eCRFs |

| **Day 9 (±1 day) of [Visit 3]** |
| --- |
| * **Efficacy evaluation (for close contacts)** * Influenza symptom score (evaluated every day during the trial) * Body temperature measurement (armpit) (measured every day during the trial) * Influenza virus nucleic acid test |
| * **Safety and other assessments (for close contacts)** * Vital signs * Adverse events/serious adverse events/adverse reactions |
| * **Other related work** * Recording of concomitant medications * Recover diary cards * Economic data collection, including: Direct medical expenses (drug expenses, inspection fees, service items expenses, nursing fees, registered bed fees, etc.), direct non-medical expenses (transportation expenses, accommodation expenses, diet expenses, nutritional support expenses), lost days in this course of disease, patient health status assessment (infection, severity (mild, moderate, and severe), hospitalization, ICU use, death, and complications) * Completion of eCRFs |

| **Day 30 (±3 days) of [Visit 4] (for close contacts)** |
| --- |
| * Economic data collection, including: direct medical expenses (drug expenses, inspection fees, service items expenses, nursing fees, registered bed fees, etc.), direct non-medical expenses (transportation expenses, accommodation expenses, diet expenses, nutritional support expenses), lost days in this course of disease, patient health status assessment (infection, severity (mild, moderate, and severe), hospitalization, ICU use, death, and complications) * Completion of eCRFs |

1.3 Study process table

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Screening period** | **Treatment period** | | **Follow-up period** | |
| Visit cycle | Visit 0 | Visit 1 | Visit 2 | Visit 3 | Visit 4 |
| Visit time | **-2~0 day** | **Day 3**  **(±1 day)** | **Day 5**  **(±1 day)** | **Day 9**  **(±1 day)** | **Day 30**  **(±3 days)** |
| **Basic medical history** | | | | | |
| Index cases and close contacts  Informed consent | ● |  |  |  |  |
| Rapid detection of influenza virus antigen in index cases | ● |  |  |  |  |
| Detection of influenza virus nucleic acid in index cases | ● |  |  |  |  |
| Detection of novel coronavirus antigen in index cases | ● |  |  |  |  |
| Detection of novel coronavirus antigen in index cases | ● |  |  |  |  |
| Detection of novel coronavirus antigen in close contacts | ● | ● | ● |  |  |
| Detection of novel coronavirus nucleic acid in close contacts | ● | ● | ● |  |  |
| Demographic data of index cases and close contacts | ● |  |  |  |  |
| General clinical data of index cases and close contacts | ● |  |  |  |  |
| **Effectiveness evaluation (for close contacts)** | | | | | |
| Influenza symptom score | ▲ | ▲ | ▲ | ▲ |  |
| Temperature measurement (armpit) | ▲ | ▲ | ▲ | ▲ |  |
| Rapid detection of influenza virus antigen | ▲ |  |  |  |  |
| Influenza virus nucleic acid test | ● | ● | ● | ● |  |
| **Safety and other assessments (for close contacts)** | | | | | |
| Vital signs | ● | ● | ● | ● |  |
| Physical examination | ● |  | ● |  |  |
| Urine pregnancy test (women of childbearing age only) | ● |  |  |  |  |
| Blood routine examination | ● |  | ● |  |  |
| Routine urine test | ● |  | ● |  |  |
| Biochemical examination of liver and kidney functions | ● |  | ● |  |  |
| Resting electrocardiogram | ● |  | ● |  |  |
| Adverse events/serious adverse events/adverse reactions | ● | ● | ● | ● | ● |
| **Other work** | | | | | |
| Record the time of starting drug delivery | ● |  |  |  |  |
| Record the end time of medication |  |  | ● |  |  |
| Recording of concomitant medications | ● | ● | ●\* | ● |  |
| Issue diary cards | ● | ● | ● |  |  |
| Recover diary cards |  | ● | ● | ● |  |
| Issue investigational drugs | ● |  |  |  |  |
| Recover surplus investigational drugs and diary cards |  |  | ● |  |  |
| Economic data collection |  | ● | ● | ● | ● |
| Completion of eCRFs | ● | ● | ● | ● | ● |

[Note]

① Close contacts are randomly enrolled on the “Day”, and The day of taking medicine is “Day 0”. The day of randomly enrolling and the day of taking medicine can be the same day.

② End of trial: a. Close contacts complete the relevant examination and evaluation of interview 3 in the study schedule; b. Close contacts have serious adverse events, which are judged by investigators to be inappropriate to continue to participate in the study;

③ Inspection window period: The screening period is 2 days, and the visiting window period is ±1 day.

④▲: Record once during screening examination and before random enrolling. If screening examination and random enrolling are on the same day, it is only necessary to record once; Record it before 22:00 every night.

⑤ \* Record the medication during influenza in the index cases by telephone interview.

# 2. Study Background

## 2.1 Study basis

Seasonal epidemics and occasional outbreaks of human influenza virus cause heavy morbidity and death burden in the world [1]. Globally, there are an estimated 1 billion influenza cases every year, including 3-5 million severe cases and 290,000-650,000 deaths due to influenza-related respiratory symptoms. Influenza vaccination is the most important and effective way to prevent the incidence of different risk groups [2], but it needs to be injected at least 2 weeks in advance to produce effective antibodies in the body. Once influenza occurs, neuraminidase inhibitors such as oseltamivir and zanamivir have been successfully used for influenza prevention in different scenarios. But the side effects associated with oseltamivir, including nausea, vomiting, diarrhea, headaches and psychotic symptoms, limit their widespread use in community influenza prevention [3-5]. In addition to vaccination and neuraminidase inhibitors such as oseltamivir and zanamivir, seasonal preventive clinical trials such as oral vitamin D and green tea gargle have been carried out abroad [6,7], but there is no clinical study report related to traditional Chinese medicine so far. Traditional Chinese medicine has been widely used to treat influenza-like diseases [8]. According to the theory of traditional Chinese medicine, influenza belongs to the category of warm disease “exogenous fever” and “epidemic disease”. Influenza disease is caused by evil and epidemic poison, among which wind-heat poison invasion is the most common. Lianhua Qingwen Capsules consists of 11 medicines, including Forsythia suspensa, Honeysuckle, Ephedra sinica (roasted), bitter almond (stir-baked), Gypsum, Radix Isatidis, Male Fern Rhizome, Houttuynia cordata Thunb, Patchouli, Rhubarb, Menthol and Glycyrrhiza uralensis Fisch. It has the effects of clearing plague and detoxifying and releasing lung and expelling heat, and is mainly suitable for treating influenza, which belongs to heat toxin attacking lung [9]. Laboratory studies have found that Lianhua Qingwen Capsules can inhibit the early infection of virus in mice, including reducing the gene expression of IL-6, IL-8, TNF-α, IP-10 and MCP-1 caused by virus [10]. Clinical meta-analysis shows that Lianhua Qingwen Capsules is superior to oseltamivir and ribavirin in curative effect and has low side effects [11, 12]. Studies also show that Lianhua Qingwen Capsules can shorten influenza A symptoms (fever, cough, sore throat and body pain) compared with oseltamivir, and their antiviral effects are equivalent [13]. The results of a Meta-analysis [12] show that the combination of Lianhua Qingwen preparation and oseltamivir phosphate is better than oseltamivir phosphate alone, and can shorten the antipyretic time; in terms of clinical effectiveness, the combination effect is better; the relief time of muscle pain, sore throat, cough and nasal congestion and runny nose in the experimental group were shorter than those in the control group, suggesting that the combined scheme may be faster in relieving symptoms; and there was no significant difference in the time of virus turning negative between the two groups. The Clinical Practice Guide for Treating Influenza with Traditional Chinese Medicine (2021) [13] strongly recommends Lianhua Qingwen Capsules for treating influenza.

Influenza prevention in the environment of people living together is an important link in community influenza prevention. The study predicts that a large proportion of community disease transmission occurs in the family environment [14]. Virus gene sequencing studies show that more than 95% of infections occur through close family contact [15]. Therefore, it is a feasible and common method to study the epidemic and transmission of influenza and related prevention by taking the people living together as a unit (including families, dormitories, etc.).

## 2.2 Preclinical studies

### 2.2.1 Introduction to study drugs

The main components of Lianhua Qingwen Capsules include Forsythia suspensa, Honeysuckle, Ephedra sinica (roasted), bitter almond (stir-baked) Gypsum, Radix Isatidis, Male Fern Rhizome, Houttuynia cordata Thunb, Patchouli, Rhubarb, Menthol and Glycyrrhiza uralensis Fisch. It has the effects of clearing plague and detoxifying and releasing lung and expelling heat. It is used for the treatment of influenza with heat-toxicity attacking the lung. The symptoms include fever or high fever, aversion to cold, muscle soreness, nasal congestion and runny nose, cough, headache, dry throat and sore throat, red tongue, yellow or greasy fur, etc. In February 2020, Lianhua Qingwen Capsules (granules) was listed in *Diagnosis and Treatment Plan for Novel Coronavirus Pneumonia (Trial Version 6)* issued by National Health Commission of the People’s Republic of China. In April, 2020, the *Approval Document of Drug Supplement Application* issued by the State Food and Drug Administration shows that Lianhua Qingwen Capsules (granules) produced by Yiling Pharmaceutical has been approved to be used for fever, cough and fatigue caused by mild and common type of COVID-19 virus pneumonia, and the course of treatment is 7 to 10 days.

### 2.2.2 Pharmacological/Pharmacodynamic studies

1. Effect on influenza virus pneumonia in mice: Mice are randomly divided into 6 groups, 10 males in each group, which are normal control group, model control group, small dose group of Lianhua Qingwen Capsules (1.5 g crude drug/kg, equivalent to 4.5 times human clinical dosage), middle dose group of Lianhua Qingwen Capsules (3.0 g crude drug/kg, equivalent to 9 times human clinical dosage), large dose group of Lianhua Qingwen Capsules (6.0 g crude drug/kg, equivalent to 18 times human clinical dosage) and positive drug moroxydine hydrochloride group (40 mg/kg, equivalent to 9 times of human clinical dosage). The administration group is continuously administered by intragastric administration of 0.2 mL/10 g body weight once a day for 7 days. The model control group is administered the same amount of sodium carboxymethylcellulose, and then infected with influenza virus lung adaptation strain FM115LD50, 0.05 mL per mouse by nasal drops under shallow ether anesthesia 30 minutes after administration on the third day. The mice are dissected 96 hours after infection, the lungs are taken and weighed, and the lung index is calculated. *Student’s t test* is used to compare the differences among the groups. The results show that the lung index of mice in the model control group is significantly higher than that in the normal control group (*P* < 0.01), which indicates that nasal influenza virus has obviously caused lung lesions in mice. The lung indexes of mice in Lianhua Qingwen Capsules (1.5 g crude drug/kg, 3.0 g crude drug/kg, 6.0 g crude drug/kg) and moroxydine hydrochloride (40 mg/kg) groups are significantly smaller than those in model control group (*P* < 0.01). Lianhua Qingwen Capsules (1.5 g crude drug/kg, 3.0 g/kg, 6.0 g crude drug/kg) has obvious inhibitory effect on influenza virus pneumonia in mice.
2. Inhibition of influenza A H3N2 virus in vitro: Mo Hongying et al. [16] studied the anti-influenza A virus effect of Lianhua Qingwen Capsules in vitro. Using ribavirin as a positive control drug, the inhibitory effect of Lianhua Qingwen Capsules on human influenza A virus H3N2 in vitro and its time-effect relationship are determined by crystal violet staining of surviving cells. Results: Lianhua Qingwen Capsules has multi-link anti-influenza virus effects, comprehensive inhibition, prevention of virus adsorption, inhibition of replication and proliferation after virus adsorption and direct killing of virus. The half effective concentrations (EC50) of these four effects are 0.042, 0.031, 0.051 and 0.050 g/mL, respectively, and the preventive administration mode has the strongest anti-influenza virus effect. With the prolongation of drug action time, the antiviral efficacy of Lianhua Qingwen Capsules at low concentration decreases, while its antiviral ability remained basically unchanged at high concentration (≥ 0.031 g/mL). At the same time, Lianhua Qingwen Capsules can obviously reduce the infectivity of virus, which indicates that Lianhua Qingwen Capsules has obvious anti-influenza A virus effect in vitro.
3. The Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences adopted three different administration methods: Pretreatment, co-treatment and post-treatment. MDCK cells were pretreated for 24 hours, infected with virus for 1 hour, incubated with virus solution for 1 hour, incubated with virus solution for 1 hour, and then incubated with drugs. They were divided into Lianhua Qingwen Group and Tamiflu Group. The therapeutic index was TD50 (half toxic concentration)/IC50 (half effective concentration), and TD50 and IC50 were calculated by Reed-Muench method. The test was terminated after the number of cytopathic changes in virus control holes exceeded 4+. The results show that Lianhua Qingwen Capsules can prolong the average survival time of mice infected with H1N1 virus, reduce the lung index of mice infected with H1N1 virus, and alleviate the inflammatory lesions of lung tissue caused by virus. The therapeutic indexes of Lianhua Qingwen Capsules by three administration methods are about one time higher than that of Tamiflu, which provides an objective experimental basis for Lianhua Qingwen Capsules to treat influenza A (H1N1) [17].

Wang Baoning et al. [18] observed the anti-influenza A virus effect of Qingrejiedu Oral Liquid in BALB/c mice. The mouse adaptive strain of influenza A (H1N1) virus (FM1, National Institute for Viral Disease Control and Prevention, China CDC) was inoculated and cultured in allantoic cavity of chicken embryo. BALB/c mice were randomly divided into normal control group, influenza virus infection model group, ribavirin tablet group, Lianhua Qingwen Capsules group and Qingrejiedu Oral Liquid high, medium and low dose groups. Mice infected with influenza virus were administered by intragastric administration. The median lethal dose (LD50) of influenza virus was measured, and the anti-influenza effect of Qingrejiedu Oral Liquid was observed by taking survival situation, death protection rate and prolonged life rate as indexes. The results showed that each dose group of Qingrejiedu Oral Liquid can alleviate the symptoms of infected mice. The death protection rate was 50%~60%. The life prolongation rate was 61.56%~73.84%. Compared with ribavirin tablets and Lianhua Qingwen Capsules, there was no significant difference.

1. Inhibition of influenza virus and parainfluenza virus Guo Hai et al. [19] observed the effect of Lianhua Qingwen Capsules on lung index of mice infected with influenza virus FM1 and parainfluenza virus Sendai strain. Mice were infected with influenza virus FM1 and parainfluenza virus Sendai strain by nasal drops. They were randomly divided into normal control group, model control group, ribavirin group, high, Lianhua Qingwen Capsules middle and low dose groups. The general conditions and lung indexes of mice were observed. Lung index = mouse lung weight (g)/mouse body weight (g) × 100%, and lung index inhibition rate = (average lung index of control group - average lung index of experimental group)/average lung index of control group × 100%. Results: The inhibition rates of high, middle and low doses of Lianhua Qingwen Capsules on lung index of mice infected with influenza virus FM1 were 12.23%, 27.13% and 28.19%, respectively, and the inhibition rate of ribavirin was 53.72%. The low dose of Lianhua Qingwen Capsules can decrease the lung index of mice infected with influenza virus FM1 (*P* < 0.05). The inhibition rates of the middle and low doses of Lianhua Qingwen Capsules on the lung index of mice infected with Sendai strain of parainfluenza virus were 25.00% and 17.65%, respectively, and that of ribavirin was 22.00%. Lianhua Qingwen Capsule can significantly reduce the increase of lung index of mice infected with Sendai strain of parainfluenza virus (*P* < 0.05, *P* < 0.01). The results showed that Lianhua Qingwen Capsules has inhibitory effect on lung damage of mice infected with influenza virus FM1 and parainfluenza virus Sendai strain.

### 2.2.3 Toxicology study

1. Acute toxicity test (N/A)
2. Long-term toxicity test: (N/A)
3. Safety evaluation results

Wang Yanxun et al. [20] systematically evaluated the clinical safety of Lianhua Qingwen preparation by means of systematic review and Meta-analysis. Methods: China Biology Medicine disc (CBM), Chinese Academic Journal Full-text Database (CNKI), Cochrane Library, MEDLINE and EMBASE were searched to collect clinical literatures of randomized controlled trials (RCT) of Lianhua Qingwen Capsules and Lianhua Qingwen Granules. The search time was from January 2003 to May 2013. Results: 40 clinical literatures of RCT are included, including 2,592 cases in the experimental group and 2,314 cases in the control group. The included literatures are classified according to the diseases, including 19 articles about influenza, 8 articles about acute upper respiratory tract infection, 6 articles about hand-foot-mouth disease, 1 article about herpes zoster, 2 articles about pulmonary infection, 1 article about adjuvant treatment of acute bronchitis, 1 article about acute tonsillitis, 1 article about chronic pulmonary heart disease and 1 article about stroke. There are 26 literatures using Lianhua Qingwen preparation alone and 14 literatures using Lianhua Qingwen preparation together with other drugs, and the course of treatment is 3~7 days. According to the dosage forms of Lianhua Qingwen preparation, there are 34 articles about Lianhua Qingwen Capsules and 6 articles about Lianhua Qingwen Granules. Adverse reactions occurred in 63 cases in the experimental group, and the incidence of adverse reactions was 2.4%. Adverse reactions occurred in 100 cases in the control group, and the incidence of adverse reactions was 4.3%. The incidence of adverse reactions in experimental group and control group was RR=0.562, 95% CI=0.412~0.767. It was reported in 24 literatures: Adverse reaction subgroup analysis, RR=0.62, 95% CI=0.46~0.82; adverse reaction subgroup analysis in digestive system, RR=0.70, 95% CI=0.50~0.97. It was suggested that the incidence of adverse reactions in digestive system of Lianhua Qingwen preparation was lower than that of other control groups. The common adverse reactions of Lianhua Qingwen preparation mostly involve digestive system, mainly manifested as nausea, diarrhea, vomiting and abdominal pain, which are extremely rare in skin and laboratory examination. The above adverse reactions are mild and can be relieved after drug withdrawal, indicating that Lianhua Qingwen preparation has good safety. Conclusion: The common clinical adverse reactions of Lianhua Qingwen preparation are gastrointestinal reactions, and the incidence of adverse reactions in different diseases is significantly lower than that in the control group.

### 2.2.4 Overview of past clinical trials

(1) Phase II clinical study on the treatment of influenza [21]

In this clinical trial, 240 cases were enrolled, 12 cases were dropped, 5 cases were eliminated and 223 cases were completed. The results showed that the curative effect of syndrome, body temperature, single symptom disappearance rate, fever onset time and body temperature recovery rate in the experimental group were higher than those in the control group. The effective rates of syndrome curative effect in the experimental group and the control group were 74.6% and 57.4% respectively, and the difference between the two groups was statistically significant (*P* < 0.01); the curative effect rate of body temperature was 72.8% in experimental group and 54.8% in control group, respectively, and the difference of the effective rates was statistically significant (*P* < 0.01); the fever rates of experimental group and control group were 93.0% and 80.0% respectively, the rates of aversion to cold were 89.5% and 76.5% respectively, the rates of dry throat or sore throat were 70.5% and 49.5%, the rates of muscle soreness were 80.7% and 65.2%, the rates of cough were 42.5% and 29.8%, respectively, and the difference between the two groups was statistically significant (*P* < 0.05 or *P* < 0.01); the onset time of fever was (3.81 ± 3.25) hours and (5.52 ± 4.49) hours in the experimental group and the control group respectively, and there was significant difference in the onset time of fever between the two groups (*P* < 0.01); the normal rate of body temperature was 93.8% in experimental group and 82.9% in control group, and there was significant difference between the two groups (*P* < 0.05).

(2) Phase III clinical study on the treatment of influenza

In this clinical trial, 440 cases were enrolled, 21 cases were dropped, 9 cases were eliminated and 410 cases are completed. The results showed that the curative effect of syndrome, body temperature, single symptom disappearance rate, fever onset time and body temperature recovery rate in the experimental group were higher than those in the control group. The effective rates of the treatment group and the control group were 78.1% and 59.0% respectively, and the difference between the two groups was statistically significant (*P* < 0.01); the curative effect rate of body temperature was 72.7% in experimental group and 57.1% in control group, respectively, and the difference of the effective rates was statistically significant (*P* < 0.01); the fever rates of experimental group and control group were 92.1% and 79.0% respectively, the rates of aversion to cold were 91.4% and 81.9% respectively, the rates of dry throat or sore throat were 66.0% and 50.0%, respectively, and the difference between the two groups was statistically significant (*P* < 0.01); and the rates of muscle soreness were 81.0% and 70.5%, the rates of cough were 44.4% and 34.4%, respectively, and the difference between the two groups was statistically significant (*P* < 0.05). The onset time of fever in experimental group and control group was (3.98 ± 3.03) hours and (5.57 ± 3.94) hours respectively, and the difference was statistically significant (*P* < 0.01); and the normal rate of body temperature was 93.5% in experimental group and 82.2% in control group, and there was significant difference between the two groups (*P* < 0.01).

(3) Clinical report on the treatment of influenza

Duan Zhongping et al. [22] reported that in a randomized, double-blind, multicenter clinical trial conducted in comparison with western medicine oseltamivir phosphate, 244 patients with influenza A (H1N1) who were diagnosed by virology, aged 16~65 years, body temperature (axillary temperature) ≥ 37.4℃ and course of disease within 36 hours were randomly divided into Lianhua Qingwen Capsules Group (n=122) and Oseltamivir Phosphate Group (n=122), which were administered for 5 days and observed for 7 days. There was no significant difference between the two groups (*P* > 0.05) in general data such as gender, age, course of disease, general physical examination, total score of influenza symptoms before treatment, single analysis index and laboratory examination index, and the baseline equilibrium was comparable. Results: ① The remission time of flu-like symptoms: The median of Lianhua Qingwen Capsules group and Oseltamivir Phosphate Group were 69 hours and 85 hours respectively, and the 95% CI confidence intervals were 63.00~84.00 and 72.00~90.00 respectively. The absolute value of the difference between the median of the two groups was less than the non-inferior limit (24h), and there was no difference between Lianhua Qingwen Capsule and oseltamivir phosphate. ② The time of virus nucleic acid negative-conversion time: The Lianhua Qingwen Capsules group and Oseltamivir Phosphate Group were (108 ± 36) h and (101 ± 34) h, so there was no significant difference between two groups (*P* > 0.05). ③ The antipyretic time: The Lianhua Qingwen Capsules group and Oseltamivir Phosphate Group were (17 ± 14) h and (23 ± 17) h, and the difference between the two groups was statistically significant (*P* < 0.05). The Lianhua Qingwen Capsules is superior to oseltamivir phosphate. The results showed that there was no difference between Lianhua Qingwen Capsules and oseltamivir phosphate in the time of virus nucleic acid negative-conversion time and the time of influenza symptom relief, but Lianhua Qingwen Capsules can significantly reduce the severity of disease and the duration of symptoms, including fever, cough, sore throat and fatigue (*P* < 0.05); and the drug tolerance of Lianhua Qingwen Capsules is good, and no serious drug-related adverse events have been found in the study.

Dai Yuelong et al. [23] studied the therapeutic effect of Lianhua Qingwen Capsules on seasonal influenza with different TCM syndromes. 793 cases of seasonal influenza were included in the study, including 451 cases in exogenous wind-heat group and 342 cases in exogenous wind-cold group, which were randomly divided into Lianhua Qingwen Capsules treatment group and compound paracetamol and amantadine capsule control group, and the duration of symptoms and signs and the occurrence of adverse reactions of each group were compared and analyzed. Results: The symptoms of the patients in the Lianhua Qingwen Capsules treatment group were relieved quickly, and the duration of fever was significantly shorter than that in the compound paracetamol and amantadine capsule control group (2.1 ± 0.9) d vs (3.3 ± 1.2) d (*P* < 0.01). (2) The symptoms of the wind-heat treatment group were relieved faster than those of the control group, and the duration of fever in the wind-cold treatment group was shorter than that in the control group (2.2 ± 1.0) d vs (3.3 ± 1.4) d (*P* < 0.01), but the degree of symptom relief was similar to that of the control group, so there was no significant difference; (3) Lianhua Qingwen Capsules was well tolerated, and the main adverse reaction was diarrhea, with a low incidence and most of them were transient. The results showed that Lianhua Qingwen Capsules is effective in treating seasonal influenza, especially for patients with exogenous wind-heat, and has good tolerance.

Zheng Xiaohui et al. [24] observed the efficacy and safety of Lianhua Qingwen Capsules in treating children’s influenza. 128 children with influenza were randomly divided into observation group and control group. The children in the observation group were treated with Lianhua Qingwen Capsules, 0.70 mg each time, 3 times a day; and the children in the control group were treated with Shuanghuanglian Oral Liquid, 10 mL each time, twice a day. Children in both groups were treated for 7 days. The scores of flu symptoms, the average time of cold recovery and fever reduction, the efficacy of fever reduction, clinical efficacy and adverse reactions were observed in the two groups. Results: After treatment, the total clinical effective rate of the observation group was 93.75%, which was higher than that of the control group (90.63%), but there was no significant difference between the two groups (*P* > 0.05); the total effective rate of antipyretic was 85.94% in observation group and 62.50% in control group (*P* < 0.05); the average time of cold recovery and fever reduction in the observation group was (49.38 ± 12.88) h and (20.68 ± 14.12) h, which were significantly lower than those in the control group (53.96 ± 11.79) h and (25.77 ± 13.96) h (*P* < 0.05); the scores of headache, sore throat, dry throat and muscle soreness in the observation group were significantly lower than those in the control group, and the difference between the two groups was statistically significant (*P* < 0.05). No serious adverse reactions occurred in the two groups of children during the treatment. The results showed that Lianhua Qingwen Capsules had a better curative effect in treating influenza in children, and could effectively relieve symptoms such as headache, sore throat, muscle soreness, etc., with shorter cure time and antipyretic time, and better safety.

(4) Study on prevention of COVID-19

Xiaowei Gong [25] et al. conducted a clinical trial of Lianhua Qingwen Capsules for the prevention of COVID-19. In the trial, a total of 1,976 subjects were enrolled, including 1,101 in the treatment group and 875 in the control group. Studies have shown that Lianhua Qingwen Capsules can prevent the infection of COVID-19 in close contacts. Among 13 patients with positive nucleic acid test results, 1 had mild symptoms and others had asymptomatic infections. The positive rates of nucleic acid testing in the treatment group and the control group were 0.27% and 1.14%, respectively, and the result of the former was significantly lower than that of the latter (*MD*: −0.87%; 95%CI: −1.83~−0.13; P=0.0174). Among the close contacts with patients with COVID-19 infection, the positive rates of nucleic acid testing in the treatment group and the control group were 6.45% and 11.43%, respectively, without significant difference between them (P=0.6762); while among the secondary close contacts, the positive rates of nucleic acid testing in the treatment group and the control group were 0.09% and 0.71%, respectively, and the result of the former was significantly lower than that of the latter (P=0.0485). No serious adverse events occurred in this study; Lianhua Qingwen Capsules were well tolerated for the prevention of COVID-19 infection.

Yunfeng Qiao et al. [26] conducted a prospective, pragmatic cluster randomized, and parallel controlled study on the preventive efficacy of Lianhua Qingwen on close contacts of COVID-19. From 199 quarantine areas in Changchun, 24,196 close contacts were randomly included. In the control group, there were 5,331 subjects in the control group, of which, 597 subjects turned positive in nucleic acid testing, with a positive conversion rate of 11.20%; there were 18,865 subjects in the Lianhua Qingwen group, of which, 979 subjects turned positive in nucleic acid testing, with a positive conversion rate of 5.19%, which was 53.66% lower than that in the control group (P<0.01).

Macau University of Science and Technology organized the study on the effect of Lianhua Qingwen on the prevention of COVID-19 using the data of Langfang, Hebei Province. In order to evaluate the preventive efficacy of Lianhua Qingwen on COVID-19, a transmission dynamics model based on the efficacy of Lianhua Qingwen was proposed; the effect of drug intervention was added to the basic SEIR infectious disease model, and then the epidemic situations before and after Lianhua Qingwen was taken were predicted and compared. The results showed that, according to the real epidemic data, the epidemic situations were controlled on April 1, 2022, and the cumulative number of infected people was 3,410. When Lianhua Qingwen was taken, the time of epidemic control was 25 days earlier than that without taking Lianhua Qingwen, and the infection scale was decreased by 52.9%.

## 2.3 Risk-benefit assessment

### 2.3.1 Known potential risks

Lianhua Qingwen Capsules used in this study are Chinese herbal medicine compound preparations that have been marketed for many years. The relevant pharmacological and toxicological studies show that Lianhua Qingwen Capsules have high safety. According to the previous clinical trials, no serious adverse reactions have occurred after Lianhua Qingwen Capsules are taken. Therefore, subjects are at a low risk after taking the investigational drug in this study.

### 2.3.2 Known potential benefits

Lianhua Qingwen Capsules have a definite curative effect on seasonal influenza. Previous studies have shown that its antiviral efficacy is equivalent to that of oseltamivir. Subjects who have taken Lianhua Qingwen Capsules may be at a low risk of secondary infection with seasonal influenza.

### 2.3.3 Potential risk-benefit assessment

The target population of this study is people who have close contact with those with seasonal influenza. Presently the seasonal influenza is prevented by vaccination and taking antiviral drugs. In this study, vaccinated subjects are excluded, and the prevention of influenza with antiviral drugs has not been widely accepted due to its side effects. Therefore, Lianhua Qingwen Capsules are used to prevent influenza in this study, which will not compromise the relevant rights and interests of submits but may achieve a preventative effect. Previous studies have shown that the investigational drugs are effective and safe and subjects will not face greater health risks.

In consideration of the study-related risks, the Sponsor will apply for insurance coverage for subjects or offer compensations for study-related damages according to regulatory requirements.

In addition, the safety assessment and inspection is formulated in this study to ensure that Investigators can observe the adverse events of the subjects in a timely manner and carry out symptomatic treatment.

Based on the above analysis, the study design complies with the ethical requirements.

# 3. Study Objectives and Efficacy Endpoints

## 3.1 Study objectives

To evaluate the effectiveness, safety and economy of preventive efficacy of Lianhua Qingwen Capsules on close contacts of seasonal influenza in a clustered environment.

## 3.2 Efficacy endpoints

### 3.2.1 Primary efficacy endpoints

1. The secondary infection risk (SIR) of influenza of close contacts taking Lianhua Qingwen Capsules or placebo within 9 days (±1 day) after randomization, i.e. the proportion of close contacts with secondary transmission of influenza, including symptomatic and asymptomatic subjects.

Definition of secondary transmission of influenza: Secondary transmission is inferred to be confirmed as influenza-positive by RT-PCR testing and the virus subtype of any nasal swab or throat swab collected during the study period is consistent with the index case.

Baseline: Defined as the total number of close contacts in the cohort

Calculation: Secondary infection risk (SIR) on Day 9 (±1) = Number of close contacts with one positive result (+) of the influenza virus PCR assay within 9 days (±1 day) after taking the medicines in the cohort/ total number of close contacts in the cohort

### 3.2.2 Secondary efficacy endpoints

1. The proportion of infected clustered units in all clustered units on days 3, 5, and 9 (±1) after randomization.

Definition of Infected Cluster: PCR (+) of any close contact participating in this study within the clustered unit, which is defined as an Infected Unit.

Baseline: Defined as the number of clustered units in the cohort

Calculation: Proportion of infected clustered unit on Day N of treatment= Number of infected clustered units on Day N of treatment on the cohort/ number of clustered units in the cohort

1. The proportion of PCR (+) of all close contacts (sum of symptomatic and asymptomatic) at days 3, 5, 9 (±1) after randomization.

Baseline: Defined as the total number of close contacts in the cohort.

Calculation: Proportion of close contacts with positive PCR assay result (+) on Day N of treatment= Number of close contacts with positive PCR assay result (+) on Day N of treatment in the cohort /total number of close contacts in the cohort

1. Proportion of (symptomatic) close contacts with positive PCR assay result (+) on Days 3, 5, 9 (±1) after randomization

“Symptomatic” is defined as the presence of at least one influenza-like symptom with an influenza symptom score of ≥1;

Baseline: Defined as the total number of close contacts in the cohort.

Calculation: Proportion of (symptomatic) close contacts with positive PCR assay result (+) on Day N of treatment = Number of symptomatic close contacts with positive PCR assay result (+) on Day N of treatment in the cohort /total number of close contacts in the cohort

1. Comparison of the mean scores of influenza-like symptoms at the first appearance of secondary transmission cases

Calculation: Mean value of the score for initial influenza-like symptoms in the cases of secondary transmission = Total score for initial influenza-like symptoms in the cases of secondary transmission in the cohort/total number of symptomatic cases of secondary transmission in the cohort

1. The proportion of cases of secondary transmission that require taking other drugs for influenza

Calculation: Proportion of cases of secondary transmission requiring taking other medicines =Number of cases of secondary transmission requiring taking other medicines = total number of symptomatic cases of secondary transmission in the cohort

### 3.2.3 Subgroup analysis

1. The preventive efficacy of Lianhua Qingwen Capsules in different virus subtypes is analyzed hierarchically.

Stratification factor: Influenza virus subtype

Analysis indicators: SIR of influenza on Day 9 (±1), proportion of (symptomatic and asymptomatic) close contacts with positive PCR assay result (+) on Days 3, 5, 9 (±1), proportion of (symptomatic) close contacts with positive PCR assay result (+) on Days 3, 5, 9 (±1).

Baseline: Defined as the total number of close contacts whose index case is type \* influenza virus in the cohort

Calculation: SIR of type \* influenza on Day 9 (±1) = Number of close contacts with one positive result (+) of type \* influenza virus PCR assay within 9 days (±1 day) after taking the medicines in the cohort/ total number of close contacts whose index case is type \* influenza virus in the cohort

Proportion of close contacts with positive result (+) of type \* influenza virus PCR assay on Day N of treatment = Number of close contacts with positive result (+) of type \* influenza virus PCR assay on Day N of treatment in the cohort/ total number of close contacts whose index case is type \* influenza virus in the cohort

Proportion of symptomatic close contacts with positive result (+) of type \* influenza virus PCR assay on Day N of treatment = Number of symptomatic close contacts with positive result (+) of type \* influenza virus PCR assay on Day N of treatment in the cohort/ total number of close contacts whose index case is type \* influenza virus in the cohort

1. Taking whether the index case takes antiviral drugs as a stratified factor, the preventive efficacy of close contacts taking Lianhua Qingwen capsules is analyzed;

Stratification factor: Whether the index case has received antiviral drug treatment during the trial

Analysis indicators: SIR of influenza Day 9 (±1), proportion of (symptomatic and asymptomatic) close contacts with positive PCR assay result (+) on Days 3, 5, 9 (±1), proportion of (symptomatic) close contacts with positive PCR assay result (+) on Days 3, 5, 9 (±1)

Baseline: Defined as the total number of close contacts whose index case has received/not received antiviral drug treatment during the trial in the cohort

Calculation: SIR of type \* influenza on Day 9 (±1) = Number of close contacts with one positive result (+) of type \* influenza virus PCR assay within 9 days (±1 day) after taking the medicines in the cohort/ total number of close contacts whose index case is type \* influenza virus in the cohort

Proportion of close contacts with positive result (+) of type \* influenza virus PCR assay on Day N of treatment = Number of close contacts with positive result (+) of type \* influenza virus PCR assay on Day N of treatment in the cohort/ total number of close contacts whose index case is type \* influenza virus in the cohort

Proportion of symptomatic close contacts with positive result (+) of type \* influenza virus PCR assay on Day N of treatment = Number of symptomatic close contacts with positive result (+) of type \* influenza virus PCR assay on Day N of treatment in the cohort/ total number of close contacts whose index case is type \* influenza virus in the cohort.

# 4. Study Design

## 4.1 Overall design

In this study, a randomized, double-blind, multicenter design method is used to evaluate the effectiveness and safety of Lianhua Qingwen Capsules in a clustered environment on close contacts of seasonal influenza.

### 4.1.1 Statistical hypothesis

The primary efficacy endpoint in this study: Secondary infection risk (SIR) of influenza of close contacts taking Lianhua Qingwen Capsules or placebo within 9 days (±1 day).

Intergroup comparison using the F test (α=0.05, two-sided test):

*H0:* The SIR of influenza on Day 9 (±1) after 5 days of treatment in the test group is equal to that of the control group;

*H1:* The SIR of influenza on Day 9 (±1) after 5 days of treatment in the test group is unequal to that of the control group.

If the SIR of influenza on Day 9 (±1) after 5 days of treatment in the test group is less than that of the control group and the difference between them is statically significant, it can be inferred that the preventative effect of Lianhua Qingwen Capsules is superior to placebo.

### 4.1.2 Sample size

Considering a 20% dropout rate, 1,100 subjects are to be included in each group of this study, with a total of 1,884 close contacts included.

See “9.2 Sample size estimation” of this protocol for the sample size estimation process in detail.

### 4.1.3 Randomization

In this study, the subjects are randomized using the Interactive Web Response System (IWRS). With the minimum dynamic randomization method, a subject randomization code table and a drug randomization code table are generated using the Interactive Web Response System (IWRS), and the index cases are randomly divided into the test group and the control group in a ratio of 1:1. Before the start of the study, the administrator of the Interactive Web Response System sends the account and password to the designated person in charge of each site. After the start of the study, the designated person in charge of the participating site logs into the system based on the assigned account and password, and enters relevant information about the cases, and then the system displays the random numbers and drug numbers assigned to the cases. The drug administrator will assign the corresponding drugs to the subjects based on the drug numbers, thereby achieving random allocation of subjects and drugs.

### 4.1.4 Blind design

In this study, a double-blind design is adopted, where the Investigators, subjects, CRA, and clinical study coordinators remain blind. All investigational drugs and placebos are packaged in a unified manner, ensuring no differences in appearance between the investigational drugs and placebos, and are blinded according to the drug random code table. The Investigators and subjects only know the random numbers and drug numbers, but do not know the treatment protocol represented by these numbers.

### 4.1.5 Study site

This study will be conducted in multiple study sites nationwide.

Responsible facility: 01, First Affiliated Hospital of Guangzhou Medical University

Participating facilities: 02-To be determined

*Note: During the clinical trial, the participating facilities may adjusted as actually required, which will not be amended in the protocol then (unless there are other amendments at the same time), but the new participating facilities should complete the protocol signature page.*

*The study sites are numbered by acronym and sorted in alphabetical order. If a new participating facility replaces the original one, the same number of the original participating facility should be kept for it; If the new participating facility is an added one, its number will be added in chronological order.*

### 4.1.6 Study grouping and intervention process

There are two groups in this study, namely the test group and the control group.

Subjects of the test group take the Lianhua Qingwen Capsules of 0.35g/capsule, 4 capsules each time, 3 times a day. Subjects of the control group take the Lianhua Qingwen Capsules Simulator (i.e. placebo) of 0.35g/capsule, 4 capsules each time, tid.

The study cycle includes a screening period and a visit period, lasting for a total of 30 days. The subjects, after being screened and meeting the inclusion/exclusion criteria, will be randomly assigned to the test group or the control group. The screening window period is 2 days, with the day of enrollment being Day 0 and the day of starting medication being “Day 1”. Randomly enrolled and starting medication can be on the same day, with a total of 5 days of medication. Subjects will be visited and undergo relevant examinations on Day 3, Day 5 and Day 9 after medication, with a visit window period of one day.

The index cases will be followed up by telephone on Day 5 to record drug combination, with a follow-up window of one day.

Close contacts will undergo a telephone visit on Day 30 to collect economic data, with a follow-up window of 3 days.

## 4.2 Rationale for study design

The primary objective of this study is to evaluate the effectiveness and safety of Lianhua Qingwen Capsules in preventing seasonal influenza in close contacts of seasonal influenza in a clustered environment. Many clinical meta-analyses show that Lianhua Qingwen Capsules is superior to Oseltamivir and Ribavirin in efficacy, and has mild side effects [11, 12]. Oseltamivir can be used for preventing influenza. Therefore, Lianhua Qingwen Capsules is selected as the investigational drug to prevent influenza.

To prevent bias, a double-blind and placebo-controlled design is adopted, and subjects are randomized using the Interactive Web Response System (IWRS), who are assigned to corresponding groups based on the random numbers generated by the IWRS

## 4.3 Rationale for dose selection

Reference is made to the Package Insert of Lianhua Qingwen Capsules for the dose of drugs in the test group, i.e. 0.35 g/capsule, 4 capsules each time, tid.

Subjects in the control group take Lianhua Qingwen Capsules Simulator of the same dose.

## 4.4 Definition of endpoint events in the study

### 4.4.1 Criteria for study completion

This study defines that a subject completes the study when reaching the following endpoint events, the investigational drug should be discontinued, and the relevant examinations and evaluations should be completed, that is, the subject will complete relevant examination and evaluation of Visit 3 in the study schedule.

### 4.4.2 Exit criteria

During the study, if the subjects experience influenza-like symptoms that are severe and unbearable, they should contact the Investigators in a timely manner, receive rapid influenza testing in the hospital, and after relevant examinations and evaluations, can be removed from the group to receive routine clinical treatment.

# 5. Study Populations

## 5.1 Inclusion criteria

Subjects are included in this study when all of the following criteria are met:

**Inclusion criteria for index cases:**

1. Gender and age are not limited;
2. At least two of the following influenza-like symptoms appear: Fever, cough, nasal congestion, sore throat, headache, runny nose and muscle or joint pain;
3. The first onset of influenza-like symptoms (a flu symptom score ≥1 point is judged as the onset of the symptom) within 48 hours;
4. Patients who are rapidly tested positive for influenza and meet the clinical diagnosis criteria of influenza;
5. In addition to the index cases, there are 2 or more adult close contacts who meet the inclusion criteria in the clustered units (i.e. the co-living environments, including the same families, school dormitories, factory dormitories and shared units, etc.);
6. Volunteers who are willing to participate in this study and sign a written ICF.

**Inclusion criteria for clustered close contacts:**

1. The index cases in the same clustered units who meet the inclusion criteria;
2. 18 ≤ age ≤ 70;
3. The result of rapid influenza virus antigen test is negative;
4. No influenza-like symptoms occur within 1 week before randomization (the total score of flu-like symptoms is 0);
5. During 9 days after randomization, persons who are expected to live with the index cases for at least 7 days and be able to participate in visits as planned;
6. Volunteers who are willing to participate in this study and sign a written ICF.

## 5.2 Exclusion criteria

Subjects are excluded from this trial when one of the following criteria is met:

**Exclusion criteria for index cases:**

1. The result of rapid COVID-19 antigen test is positive;
2. The close contacts in the clustered units who participate in this study but are tested positive for COVID-19;
3. Severe and critical patients who require hospitalization;
4. Patients with other serious clinical conditions who require hospitalization or monitoring;
5. Other patients considered by the investigator to be inappropriate to participate in this study.

**Exclusion criteria for clustered close contacts:**

1. Positive results of rapid influenza tests;
2. Pregnant perinatal and nursing women;
3. Patients combined with serious diseases of major organs or systems such as heart, brain, respiratory system, circulatory system, endocrine system, immune system, and hematopoietic system (such as congestive cardiac failure, with severity levels of III to IV by NYHA classification; significant arrhythmias or abnormal heart valves that cause hemodynamic impairment; history of unstable angina or myocardial infarction within the past 6 months; malignant tumors in the non-radiotherapy or non-chemotherapy stable period; advanced stage of pulmonary tuberculosis; severe hypertension; diabetic complications such as diabetic ketoacidosis; immunodeficiency diseases such as HIV that have not achieved immune function reconstruction; autoimmune diseases such as systemic lupus erythematosus);
4. ALT >5 ULN, AST >5 ULN or SCr >1.5 ULN in the screening results;
5. Persons who have taken Lianhua Qingwen preparation or any drugs with antiviral effect within 7 days. (Such as: Jinhua Qinggan, Qingkailing, Shufengjiedu, Yinqiaojiedu, Sangjuganmao, Banlangen, Yinhuang, oseltamivir, zanamivir and peramivir in any dosage form);
6. Persons who have been vaccinated against influenza within 6 months;
7. Persons who are allergic to the investigational drug;
8. Patients who have participated in other drug clinical trials within 1 month prior to the screening test;
9. Other patients considered by the investigator to be inappropriate to participate in this study.

## 5.3 Diagnostic criteria for seasonal influenza

Reference is made to the *Guidance of Diagnosis and Treatment for Influenza (Version 2019)* [27] in this study.

## 5.4 Screening failure

Screening failure means that a subject agrees to participate in the clinical study but does not receive the study interventions or is not included in the study because of failure to meet all the inclusion criteria or meet any one of the exclusion criteria. The data and information of subjects who fail to screening should be retained for checking by relevant departments. These data and information include Informed Consent Forms (ICFs), demographic data, and details of screening failures (such as test reports). Subjects who fail screening due to specific variable factors may be subjected to re-screening.

## 5.5 Subject recruitment

It is planned to enroll 1,884 subjects of close contacts, including 942 in each of the test group and the control group. It is estimated that the index cases are mainly from outpatient clinics of each study site. In this study, subjects will be recruited by means of recruitment advertisements in hospital departments, including but not limited to, display stands, posters, H5, electronic screen playback, etc.

**6. Study Interventions**

## 6.1 Management of study interventions

### 6.1.1 Description of study interventions

* **Lianhua Qingwen Capsules**

[Generic name] Lianhua Qingwen Capsules

[Components] Forsythia Suspensa, Honeysuckle, Ephedra sinica (roasted), bitter almond (stir-baked), Gypsum, Radix Isatidis, Male Fern Rhizome, Houttuynia cordata Thunb, Patchouli, Rhubarb, Menthol, and Glycyrrhiza uralensis Fisch.

[Functions and Indications] Clearing scourge and removing toxicity, ventilating the lung and discharging heat.

[Approval No.] GYZZ Z20040063

[Manufacturer] Shijiazhuang Yiling Pharmaceutical Co., Ltd.

* **Lianhua Qingwen Capsule Simulator**

**[Name] Lianhua Qingwen Capsule Simulator**

[Components] Medicinal starch, caramel color, sunset yellow pigment, menthol

[Manufacturer] Shijiazhuang Yiling Pharmaceutical Co., Ltd.

The above drugs are provided by Shijiazhuang Yiling Pharmaceutical Co., Ltd. The investigational drugs are prepared according to the clinical study requirements and meet the relevant specifications.

### 6.1.2 Dosage and route of administration

* **Treatment group**

Lianhua Qingwen Capsules

Dosage and administration: 4 Lianhua Qingwen Capsules (0.35 g/capsule), taken orally in the morning, noon and evening respectively, tid.

Course of treatment: 5 days

* **Control group**

Lianhua Qingwen Capsule Simulator

Dosage and administration: 4 Lianhua Qingwen Capsule Simulators (0.35 g/capsule), taken orally in the morning, noon and evening respectively, tid.

Course of treatment: 5 days

## 6.2 Management of drugs

### 6.2.1 Receipt and quantity check of drugs

The drug provider will deliver drugs to each study site through a logistics company in a unified manner, and the study site should designate a special drug administrator to receive the drugs and check the quantity.

The dispensing of drugs should be under strict management. All participating sites shall assign a person to keep the drugs and fill out the receipt and use records. During the study period, the remaining drugs and packaging should be recycled and checked in a timely manner. The CRA shall check the drug dispensing, use and recycling records regularly, and verify and deal with the exceptions at any time.

### 6.2.2 Dosage form, appearance, package and label of drugs

1. **Dosage form and appearance**

* **Lianhua Qingwen Capsule:** A hard capsule, with the contents of brownish yellow to yellowish brown granules and powder; slightly fragrant smell and slightly bitter taste.
* **Lianhua Qingwen Capsule Simulator:** A hard capsule, with the contents of brownish yellow to yellowish brown granules and powder.

1. **Drug packaging box**

* **Treatment group**

Packing specification: 0.35 g×12 granules ×2 plates/box.

* **Control group**

Packing specification: 0.35 g×12 granules ×2 plates/box.

1. **Drug labels**

Each package is attached with a label. See “Appendix 1 Packaging Box Label Format of Investigational Drugs” for detail.

### 6.2.3 Storage and stability of drugs

A management system of the investigational drugs in the study period should be established. Special cabinets are used to keep the investigational drugs, which are under the unified management of the drug administrator. A management system of the investigational drugs in the study period is established, indicating the dispensing date and random number of investigational drugs, subject’s name, and dose level, etc.

Drugs and storage requirements:

|  |  |  |
| --- | --- | --- |
| **Drug** | **Lianhua Qingwen Capsules** | **Lianhua Qingwen Capsule Simulator** |
| **Storage condition** | Preserve under well-sealed conditions, store at a temperature not more than 20℃ and protect from light. | Preserve under well-sealed conditions, store at a temperature not more than 20℃ and protect from light. |
| **Stability** | 30 months | 30 months |

### 6.2.4 Preparation and dispensing of drugs

The subjects of the index cases are randomly included in the test group or the control group at a ratio of 1:1, and the close contacts are included in the test group or the control group according to the randomization results of the index cases. The drug administrators of each site shall dispense the investigational medicinal products (IMPs) to subjects according to the subjects’ random numbers and drug numbers. When dispensing drugs, the drug administrators shall fill in the drug dispense registration form in a timely and accurate manner; each site shall assign a special person to store, dispense, recycle, record, return or recover the investigational drugs according to the management system.

Instructions for dispensing drugs: Drugs will be dispensed on the day when the subjects are enrolled. Three boxes of drugs are dispensed to each group of subjects each time.

### 6.2.5 Recycling and destruction of drugs

At the end of study, the drug administrator shall return the remaining drugs to the drug provider in a centralized manner and fill out the drug recycling and handover records. The drug provider shall destruct the investigational drugs according to the prescribed procedures, and fill out the investigational drug destruction record and archive them.

## 6.3 Randomization and blinding

The number of index cases consists of the letter A and four digits, of which, the first two digits represent the site number and the last two digits represent the serial number.

The number of close contacts consists of the letter B and six digits, of which, the first four digits represent the index case number of the subject, and the last two digits represent the serial number.

Randomization is performed on the basis of index cases and their close contacts. The eligible index cases and their close contacts will be randomly assigned to the Lianhua Qingwen group or the placebo group at a ratio of 1:1 using the Interactive Web Response System (IWRS). The random minimization method will be used to balance the number of index cases and their close contacts.

### 6.3.1 Drug random coding

The investigational drugs were blinded by the block randomization method, and dispensed through IWRS.

### 6.3.2 Blinding

The drug blinding is completed by a blinding staff member independent of this study. The blinding process should be documented and signed by all the blinding personnel, and the blind codes should be entered in the IWRS; any unblinding at will is regarded as a failure of this clinical study.

Invalidation of the double-blind trial: The breaking rate of blind codes or unblinding rate exceeds 20%.

### 6.3.3 Relevant requirements for unblinding and emergency breaking of blindness

After data entry and blind review, unblinding is implemented; after unblinding, statistical analysis of data is conducted.

Provision on unblinding: One-time unblinding for this study. After the database is locked, the Principal Investigator will file an application for unblinding, and the supplier will implement unblinding in the IWRS to identify the groups to which subjects belong.

Emergency breaking of blindness: Breaking of blindness can be considered under the following circumstances, including but not limited to:

1. When serious adverse reactions occur in patients;
2. When serious complications occur in patients;
3. When patients’ symptoms worsen and emergency measures should be taken.

When emergencies (such as SAEs, serious complications) occur in a subject and the rescue measures for this subject must be known, upon written consent of the PI, the Investigator shall log into the IWRS, select the subjects for emergency unblinding, fill out the reasons for emergency unblinding online, and click the button “OK”. After the system confirms the identity of the operator, the emergency unblinding process is completed. The group to which the subject belongs will be informed on the site and an emergency unblinding receipt will be generated. The Investigator will sign on the printed emergency unblinding receipt for confirmation, and the original copy will be kept in the study site.

Breaking of blindness is not allowed for subjects who are withdrawn due to the curative effect.

**6.4 Compliance of subjects**

At each follow-up visit, the subjects’ medications should be recorded in detail to evaluate the medication compliance of the subjects and decide whether the subjects can continue to participate in the study.

The compliance of subjects is to take medicines as required during the clinical study. Subjects should be aware of the importance of taking medicines on time, take medicines in strict accordance with the regulations, and avoid the addition of other drugs or therapies by themselves.

At the end of study, the medication compliance of subjects is calculated, and statistical analysis is performed.

Medication compliance = (Actual dosage amount/theoretical dosage amount) × 100%.

Assessment of subject compliance: When the dosage amount is between 80% and 120% of the prescribed amount, the subject compliance is good.

**6.5 Combination therapy**

### 6.5.1 Permitted general therapy

1. The index cases receive clinical routine treatment without interventions, but the medication for treatment should be recorded in detail for analysis and reporting in the summary.
2. Drugs that must be continued by close contacts with underlying diseases can continue to be taken if the investigator determines that they do not violate the provisions of contraindicated drugs and do not affect the observation of the efficacy of the investigational drug; drugs or other therapies that must be continued for comorbidities must be recorded in the case report form by drug (or other therapy) name, dosage, frequency and time of usage, etc. for analysis and reporting in the summary.

### 6.5.2 Contraindicated drugs

Close contacts are prohibited from taking antiviral drugs throughout the trial (such as: oseltamivir, zanamivir, paramivir, favipiravir, arbidol, amantadine, rimantadine, etc.); traditional Chinese medicine or Chinese patent medicine with antiviral effect other than those specified in the protocol is also prohibited (such as: any dosage form of Jinhua Qinggan, Qingkailing, Shufengjiedu, Yinqiaojiedu, Sangjuganmao, Banlangen, Yinhuang and other preparations or antiviral oral liquids). Before the close contacts develop flu-like symptoms, the following therapeutic drugs are contraindicated:

1. Antibacterial and antifungal drugs;
2. Drugs with antipyretic effect;
3. Drugs to improve cold symptoms (antihistamines: chlorpheniramine maleate, cetirizine, loratadine, etc.; expectorants: Ambroxol, bromohexine, acetylcysteine; drugs for contracting mucosas and blood vessels of upper respiratory tract: Pseudoephedrine hydrochloride; cough suppressants: Dextromethorphan hydrobromide, codeine, etc.; or compound preparations containing the above active ingredients).

### 6.5.3 Symptomatic treatment

If any close contact develops flu-like symptoms, the following symptomatic treatment can be performed after the influenza symptom score form is completed the same day:

If any close contact develop fever with a body temperature above 38.5 ℃ continuously for more than 4 hours or above 39 ℃, oral non-glucocorticoid antipyretic drugs can be used. If the non-glucocorticoid antipyretic drug is used, the date and time of each dose should be recorded. If any close contact develops other flu-like symptoms, the drugs to improve cold symptoms (except traditional Chinese medicine or Chinese patent medicine) can be taken. If the drug to improve cold symptoms is used, the date and time of each dose should be recorded.

### 6.5.4 Lifestyle considerations

Subjects are advised to avoid smoking and alcohol drinking as much as possible, and avoid spicy, cold and greasy foods throughout the study.

# 7. Study Intervention Discontinuation and Subject Discontinuation/Withdrawal

## 7.1 Study intervention discontinuation

Study intervention discontinuation does not represent study discontinuation, but the subsequent study procedures should be completed as per the study protocol. In the event that there are clinically meaningful changes after enrollment (including but not limited to deviations from baseline), the Investigator or qualified designated personnel will determine whether subject management needs to be changed, and whether adverse events (AEs) or serious adverse events (SAEs) need to be reported.

Data collected at the study intervention discontinuation include:

* Physical examination
* Vital signs
* ECG
* Blood routine
* Biochemical test of liver and kidney functions
* Concomitant medication
* Other examination indicators that need to be collected as deemed by the Investigator

## 7.2 Subject discontinuation/withdrawal from the study

Subjects who have completed the ICFs and have been screened as eligible for enrollment (i.e. having been assigned with a random number) have the right to withdraw from the clinical trial at any time. Or, if one of the following conditions occurs during the test, the subject should be treated as a drop-out/withdrawal case:

1. Severe comorbidities or special physiological changes occur to the subject during the trial, and the investigator believes that it is not suitable for this subject to continue to participate in the trial;
2. The subject shows poor compliance (e.g., taking medication against the prescribed protocol; or using the contraindicated drugs in this protocol or other therapies), and the investigator believes that it is not suitable for this subject to continue to participate in the trail;
3. The subject is unwilling to continue to participate in the trial and clearly proposes to the investigator to withdraw from the trial;
4. The subject has not explicitly proposed to withdraw from the trial, but no longer receives medication or examination and consequently misses the follow-up visits;
5. If an index case is screened as negative by influenza virus nucleic acid test, the clustered unit that this index case belongs to is withdrawn from the study;
6. The close contact is screened as positive by influenza virus nucleic acid test;
7. If an index case or a close contact is screened as positive by COVID-19 nucleic acid/antigen test, the clustered unit that this index case or close contact belongs to withdrawal from the trial;
8. Any subject who breaks blindness midway for various reasons.

The reasons for the subjects’ discontinuation or withdrawal from the study should be recorded in the “Study Completion Summary” of the CRF, and the last primary efficacy test results are carried forward to the final results for statistical analysis. The original medical records of subjects should be kept for future reference.

For subjects who withdraw from the study due to AE or adverse reactions, the Investigator should take appropriate treatment measures depending on subjects’ actual conditions to complete the last test as much as possible for analysis of effectiveness and safety. The Investigator shall keep the relevant study data of the dropout cases as an archive and for statistics of Full Analysis Set.

To ensure the compliance of subjects, the Investigator shall conscientiously implement the informed consent and explain them to subjects patiently during the clinical study, so that they are fully aware of the significance of the study and the importance of medications on time and can cooperate well during the trial.

## 7.3 Loss to follow up

If the subject does not return to the study site for the prescribed study visit, and is unable to be contacted by the Investigators of the study site, it will be considered as a loss of follow-up.

If the subject does not return to the study site for the prescribed study visit, the following actions should be taken:

1. The Investigators will attempt to contact the subjects, reschedule missed visits within 3 days before and after the scheduled visit time, explain the importance of adhering to the visit schedule to the subjects, and confirm whether the subjects are willing and/or should continue to participate in the study.
2. Before the subject is deemed to have been lost to follow-up, the Investigators will make every effort to re-contact with the subject (such as making at least three phone calls, and leaving messages on WeChat or QQ). These attempts to contact the subject will be recorded in the medical record or other original records of the subject.
3. If the subject is still unable to be contacted, he/she will be considered loss to follow-up and exit from the study.

# 8. Study Evaluation and Process

## 8.1 Basic medical history

1. Demographics data: The age, gender, smoking history, drinking history, height, weight, BMI, nationality, occupation, marital status, etc. of the subjects are recorded during the screening period.
2. General clinical data: The medical history, course, treatment history, comorbidities, and medication of the subjects are recorded during the screening period.

## 8.2 Effectiveness assessment (for close contacts)

1. Score of influenza symptoms: the subjects will be recorded once at Visit 0; during the test, clinical symptoms (fever, headache, muscle soreness, chills, fatigue, sore throat, cough, nasal congestion, and runny nose) are scored from 18:00 to 22:00 every night, and the evaluation results and evaluation time (month/day/year/hour/minute) are recorded in the score sheet. Please refer to “Appendix 2 Influenza Symptom Scoring Criteria” for the influenza symptom scoring criteria.

|  |  |  |
| --- | --- | --- |
| **Study period** | **Daily evaluation time** | **Suggested evaluation time window for “score of influenza symptoms”** |
| At night | 18:00-22:00 |

1. Body temperature measurement (under the armpit): The subject records once at Visit 0. During the visit, measure the temperature of the armpit (left or right) with a thermometer every night, and record the measurement results and time (month/day/year/hour/minute) in the scoring table. If the subject consciously experiences an increase or decrease in body temperature, they can increase the number of measurements according to their own needs.

|  |  |  |
| --- | --- | --- |
| **Study period** | **Daily temperature measurement time** | **Suggested time window for “measuring body temperature”** |
| At night | 18:00-22:00 |

1. Influenza virus nucleic acid test: The throat swab samples of the subjects are collected at Visit 0, Visit 1, Visit 2 and Visit 3, and the influenza virus typing and expression level of the samples are tested by nucleic acid RT-PCR technology.
2. Drug administration record: During the visit and follow-up, if the subject needs to take other drugs for influenza for the influenza-like symptoms, the generic names of the drugs, as well as the start time of medication and the use method and dose, should be recorded in detail. The index cases are followed up by telephone on Visit 2, with medication being recorded.

## 8.3 Safety assessment

1. Vital signs: The body temperature, heart rate, respiration and blood pressure of the subjects are measured. The index cases are tested once when screened for enrollment. The close contacts are tested once when screened for enrollment, on Day 3, Day 5, and Day 9, respectively.
2. Physical examination: Physical examinations of the five senses, chest and lungs, heart, abdomen, pelvic cavity, limbs, nerves, lymph nodes, skin, and other systems are performed. The close contacts are tested once at enrollment during the screening period and on Day 5 after medication, respectively.
3. Urine pregnancy test: Female subjects of childbearing age with childbearing potential among the close contacts are tested once during the screening period.
4. Laboratory tests:
5. Routine blood test: Test items include but not limited to red blood cell count (RBC), white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count (PLT), hemoglobin (HGB); record any other abnormalities found in the above results (if any). The close contacts are tested once during the screening period and on Day 5 after medication, respectively.
6. Routine urine analysis: Test items include but not limited to urine protein (PRO), urine glucose (GLU), urine ketone bodies (KET), urine red blood cells (URBC), urine white blood cells (UWBC); record any other abnormalities found in the above results (if any). The close contacts are tested once during the screening period and on Day 5 after medication, respectively.
7. Biochemical test of liver and kidney functions: Test items include subjects’ alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), urea/blood urea nitrogen (UREA/BUN), serum creatinine (SCr), albumin (ALB); record any other abnormalities found in the above results (if any). The close contacts are tested once during the screening period and on Day 5 after medication, respectively.
8. Resting ECG: The subjects’ resting ECG is tested. The resting ECG of close contacts is tested once during the screening period and on Day 5 after medication, respectively.
9. Adverse events/serious adverse events/adverse reactions: Observe and record them at any time during the trial period. See “8.4 Adverse events, serious adverse events and adverse reactions” for details.

## 8.4 Adverse events, serious adverse events and adverse reactions

### 8.4.1 Definition of adverse events

**Adverse event** (AE) refers to all adverse medical events that occur after the subjects receive the investigational product, which can be manifested as symptoms, signs, diseases or abnormal laboratory tests but do not necessarily have a causal relationship with the investigational product.

**Significant adverse event** refers to any adverse event that, in addition to a serious adverse event, led to the use of targeted medical measures (e.g., drug withdrawal, dose reduction, and symptomatic treatment) and significant hematological or other laboratory abnormalities.

### 8.4.2 Definition of serious adverse events

**Serious adverse events** (SAEs) refer to the following circumstances occurring after subjects have received the investigational product:

**①Death:** The event causing “death” can be definitely recorded and reported as a SAE; **②Life-threatening:** The patient is at a risk of death when an AE occurs; it does not mean that the AE may cause death when it becomes more serious; **③Subjects require hospitalization or prolonged hospital stay:** The circumstance is definitely caused by AE, excluding elective surgery, non-medical factors, etc. that lead to hospitalization; **④Permanent or severe disability or loss of function; ⑤Congenital abnormalities or birth defects:** Congenital abnormalities and deformities in the offspring of the subject; **⑥Other significant medical events:** These adverse events may not immediately threaten life or lead to death, but may cause harm to patients or may require intervention measures to prevent the occurrence of above outcomes, which should be determined based on scientific medical judgment.

### 8.4.3 Definition of adverse reactions

**Adverse drug reactions** (ADRs) refer to any harmful or unexpected reactions occurring in the clinical trials that may be related to the investigational product. The causal relationship between the investigational product and the adverse event is at least potentially reasonable, i.e. the correlation cannot be ruled out.

### 8.4.4 Classification of adverse events

#### 8.4.4.1 Severity of adverse events

1. Mild: Mild subjective symptoms can be tolerated and do not affect daily life activities; the symptoms are transient and will be relieved spontaneously during the continued medication without need of treatment.
2. Moderate: The symptoms are more obvious and affect the subjects’ daily life activities, which last for a long time and can be relieved spontaneously or relieved after symptomatic treatment. It is possible to interfere with the use of the study drugs, for example, reducing the drug dose or withdrawing drugs, etc.
3. Severe: The subject’s body functions are impaired and the subjects are unable to work and live normally. The symptoms last for a long time, and can be relieved after drug withdrawal and appropriate treatment.

The severity and intensity of adverse events should be distinguished. “Severe” is used to describe intensity, which is not necessarily a serious adverse event (SAE). For example, headache may be severe in intensity but cannot be classified as a SAE unless it meets the SAE criteria.

#### 8.4.4.2 Determination of causal relationship between adverse events and drugs

The causal relationship between adverse events and drugs should be judged by an authorized clinician. The judgment for the causal relationship should be made and rationale should be given. When an event becomes severe or constitutes a SAE, the PI or co-Investigator shall assume the main responsibility for the judgment of causal relationship and described the work in the medical records, and where necessary, organize consultation and judgment with relevant professional medical staff.

To determine the causal relationship between adverse events and drugs, considerations should be given to the following:

1. Whether there is a reasonable temporal correlation between the medication and the occurrence of AEs;
2. Whether the AE conforms to the known adverse reaction types of the drug;
3. Whether the AEs are alleviated or disappear after drug withdrawal or dose reduction;
4. Whether the same AEs occur again after the suspected drug is used again;
5. Whether the AEs can be explained by the effect of concomitant medications, progress of the patient’s condition, and the impact of other treatments.

| Five-level classification | Judgment criteria |
| --- | --- |
| Definitely related | The adverse event is clearly related to the investigational agent - i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, abates or disappears upon dose reduction or discontinuation of the drug, and reappears when the drug is administered again. |
| Probably related | The adverse event is related to the investigational agent - i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, abates or disappears upon dose reduction or discontinuation of the drug, but that could readily have been produced by a number of other factors. |
| Possibly related | The adverse event is related to the investigational agent - i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, abates or is not apparent upon dose reduction or discontinuation of the drug, but that could readily have been explained by a number of other factors. |
| Possibly unrelated | The adverse event is not related to the investigational agent - i.e. an event that does not follow a reasonable temporal sequence from administration of the study intervention, but that could possibly have been produced by a number of other factors. |
| Definitely unrelated | The adverse event is clearly not related to the investigational agent- i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible. |

When the sum of the circumstances of “definitely related”, “probably related” and “possibly related” is used as the numerator for calculation of the incidence of adverse reactions, the denominator is the number of all subjects used to evaluate safety.

#### 8.4.4.3 Expectation

Known adverse reactions:

1. Lianhua Qingwen Capsules

The previous studies show that the common adverse reactions of Lianhua Qingwen Capsules mostly involve the gastrointestinal system, with the main manifestations of nausea, diarrhea, vomiting and abdominal pain; there are rare skin and laboratory test abnormalities.

1. For adverse reactions of drugs and medical devices involved in routine clinical treatment, please refer to the Package Insert.

### 8.4.5 Assessment of adverse events, time limit and frequency of follow-up visits

#### 8.4.5.1 Observation, collection and recording

The Investigator shall inform the subjects that they should state their disease conditions after medication truthfully and avoid inducing questions. The adverse events or unexpected toxic and side effects should be observed while the curative effect is observed.

The AEs/SAEs will be collected from the first dose of the investigational drug until the visit 3. The clinical AEs occurring during the period from signing the ICFs to the first dose will be recorded in the CRFs as medical history/comorbidities rather than as AEs, unless one of the following circumstances is met: Injury/damage caused by any clinical laboratory tests; AEs caused by drug discontinuation related to the study protocol; AEs caused by drugs other than the investigational products taken as a part of treatment regimens. Only subjects’ spontaneous reports are collected beyond the time limit. The clinical AEs occurring during the period from signing the ICFs to the first dose will be recorded in the CRFs as medical history/comorbidities rather than as AEs, unless one of the following circumstances is met: ① Injury/damage caused by any clinical laboratory tests; ② AEs caused by drug discontinuation related to the study protocol; ③ AEs caused by drugs other than the investigational products (for example, basic treatment drugs) taken as a part of treatment regimens.

The collected AEs are mainly assessed through laboratory tests of safety indicators and Investigators’ consultations. When asking about AEs, the questions should be neutral, without presentation of any expected side effects because of the investigational drugs; in addition, the subjects should not be provided with a list of AEs for their selection, which will interfere with the subjects’ subjective feelings. The collected information should be compared with the baseline signs and medical history at the previous follow-up visits and at the beginning of the study. During the consultation, the information related AEs will be obtained with reference to the following questions: ① Has your previous discomfort or abnormality (if any) changed? Is it serious, or has it been resolved? ② Have you ever taken any new medicines since the last study visit? ③ Have you stopped or changed the dose or frequency of any medication you are using after the last study visit? (Any such change may produce a new AE or an ongoing AE). ④ Has your physical conditions improved or deteriorated since the last study visit?

The AEs/SAEs that have occurred should be recorded in detail, regardless of whether they are related to the investigational drug, including the name, severity, time of occurrence (time of onset of symptoms), termination time or outcome of the events, concomitant medications, use of investigational drugs, treatment measures and outcome; and the causal relationship between the event and the investigational drug should be determined in time. The event report form should be filled out, signed and dated.

Common outcomes can be described as follows:

1. Recovered/Resolved: The “date of termination of AE/SAE” should be indicated.
2. Recovering/Resolving: The event is still not fully resolved, but the patient is recovering. Follow-up is required.
3. Unrecovered/Unresolved: The event is ongoing.
4. Recovered/resolved with sequelae: Describe only when the patient may have long-lasting or life-long sequelae, for example, blindness caused by diabetes, hemiplegia after stroke. The “date of termination of AE/SAE” should be indicated.
5. Death: The “date of termination of AE/SAE” should be indicated. When an AE causes death, the time of death should be recorded.
6. Unknown: The Investigator is not aware of the AE, for example, the patient is lost to follow-up.
7. If the outcome of the AE is rated as “recovering/resolving”, or “unrecovered/unresolved “, or “unknown”, the date of AE termination may not be recorded temporarily.
8. If the AE outcome is rated as “recovered/resolved” or “recovered/resolved with sequelae”, the date of AE termination must be recorded.
9. All AEs must be followed up to determine the final outcome or to achieve a stable state.

After the patients completes the clinical study, the Investigators should follow up the outcomes of AEs that may be related to the investigational drug or be undetermined, or until they reach a stable state.

#### 8.4.5.2 Time limit and frequency of follow-up visits

All AEs/SAEs occurring during the study period should be followed up and recorded until the event ends, the state is stable or returns to the baseline state, is reasonably explained, the subjects are lost to follow up or die. In principle, the AEs/SAEs that are clearly not drug-related should be followed up and recorded until the event ends, the state is stable or returns to the baseline state, is reasonably explained, the subjects are lost to follow up or die, but no later than 6 months after visit 3.

In principle, the follow-up frequency of AEs/SAEs should be determined in the opinions of the investigator. If the event is mild in severity, the frequency of follow-up visits can be synchronized with the time point of the subject’s study visits; if subjects have completed visit 3, they should return to the hospital for follow-up visits once approximately every 2 weeks.

### 8.4.6 Judgment, reporting and management of adverse events (AEs)

AEs should be recorded and reported in strict accordance with the requirements of the IRB of each study site.

#### 8.4.6.1 Assessment of “clinical significance”

**Outlier:** The test value is beyond the laboratory normal range.

**Clinical significance (CS):** There is a difference between the test value and the normal standard value, which has a certain reference value for the clinical diagnosis of diseases.

**Non-clinical significance (NCS):** The abnormal test value may be caused by the changes in physiology or normal conditions, which has no basis and value for the disease diagnosis.

The test values are only a part of the clinical efficacy and safety. Investigators should evaluate them in combination with other assay and test results in the clinical judgment process. Consideration should be given to other assay and detect results for the clinical judgment. These considerations mainly include: ① It may be caused by external factors such as equipment; ② Whether there are literature and reports and disease association for the drugs used, etc.; ③ Slightly transient increase, which are not supported by relevant evidences and considered no significance of abnormality; ④ Obviously abnormal indicators should be checked and confirmed; and if the indicators are still abnormal, it is generally considered to be significant; ⑤ If the test values are within the reference value range or abnormal and non-significant, which are found to increase abnormally during the trial and cannot be reasonably explained, or still increase after re-examination, it is determined clinically significant.

#### 8.4.6.2 Judgment of adverse events

Clinical significance or non-clinical significance is not used as AE assessment criteria. Generally, it should be recorded and reported as AEs under the following circumstances: ① A laboratory test indicator is abnormal, accompanied by other abnormal symptoms and signs indicating aggravation; ② Events require special management, such as adjustment of investigational drugs, symptomatic treatment, and closer follow-up visit.

In this study, if the influenza symptoms (fever, headache, muscle soreness, chills, fatigue, sore throat, cough, nasal congestion, runny nose), body temperature (armpit), and nucleic acid test results of influenza virus, as efficacy evaluation indicators, are abnormal and clinically significant and do not require adjustment of interventions for symptomatic treatment, they will not be recorded and reported as AEs.

### 8.4.7 Reporting of serious adverse events (SAEs)

If a SAE occurs during the trial, the Investigator shall take necessary measures immediately to guarantee the safety of the subject, fill out the *Report of Serious Adverse Events*, and sign and date it. If the SAE develops from the AE, the Investigator shall fill out the *Adverse Event Report* in addition to the *Report of Serious Adverse Events*. The start time of the SAE should be calculated from the date when the AE is upgraded to a SAE.

The SAEs should be reported to the Sponsor and the Ethics Committee of each study site within 24 hours after the Investigator is informed (or according to the institutional/ethical requirements of each study site), and when, how and to whom this SAE is reported should be recorded in the raw data. In addition, the Sponsor shall ensure compliance of the reporting procedures required by the laws and regulations. All study sites should conduct periodic SAE summary and reporting according to the requirements of IRB of the lead site.

Hospitalization is not recorded and reported as a SAE under the following circumstances: ① Hospitalization or prolonged hospitalization due to diagnosis of existing diseases or elective surgical treatment; ② Hospitalization or prolonged hospitalization for efficacy assessment in the study; ③ Hospitalization or prolonged hospitalization due to the prescribed course of treatment for the target disease in the study.

### 8.4.8 Reporting events to subjects

N/A.

### 8.4.9 Events of special interest

N/A.

### 8.4.10 Pregnancy reporting

If a female subject or a partner of a male subject becomes pregnant from the first dose of the investigational drug to Visit 3, the investigational drug should be discontinued immediately and the Investigator should be notified; meanwhile, the event will be handled as a SAE, and followed up to pregnancy outcome (for example, termination of pregnancy or 42 days after delivery).

The event will be handled as SAE/AE if subsequent circumstances occur during the pregnancy, such as fetal/newborn congenital abnormality or malformation (SAE), spontaneous abortion (SAE), termination of pregnancy for medical reasons (AE/SAE).

## 8.5 Unexpected events

### 8.5.1 Definition of unexpected events

An adverse event is considered unexpected if its nature, severity, or frequency is inconsistent with previously described risk information for the study interventions.

**Suspected Unexpected Serious Adverse Reaction (SUSAR):** It is defined as a reaction whose nature and severity of clinical manifestations exceed the existing information available in the Investigator’s Brochure of the investigational drug, Package Insert of marketed drugs or Summary of Product Characteristics, etc.

### 8.5.2 Reporting of unexpected events

After being informed of the SAE, the Sponsor shall conduct a comprehensive analysis, evaluation and judgment on it immediately. For unexpected serious adverse reactions that are fatal or life-threatening, the Sponsor shall report it as soon as possible after being informed for the first time (the day when the Sponsor is informed is Day 0), but not later than 7 days, and report and complete follow-up information in the subsequent 8 days. For unexpected serious adverse reactions that are not fatal or life-threatening, the Sponsor shall report it as soon as possible after being informed for the first time, but not later than 15 days. After the first reporting, the Sponsor shall continue to track the serious adverse reactions and report the new information or changes to the previous report in a form of a follow-up report in a timely manner. The time limit for reporting is within 15 days after the new information is available.

The Sponsor shall report the SAE to the Drug Evaluation Center of the National Medical Products Administration and other relevant departments in accordance with the regulations, and inform them to the Ethics Committee and the Investigators of each study site.

### 8.5.3 Reporting unexpected events to subjects

If suspected unexpected serious adverse reactions occur during the trial, the Investigator shall notify the subjects during regular visits, and supplement the notification during the subsequent informed consent process.

# 9. Statistical Considerations

## 9.1 Statistical hypothesis

This study adopts the superiority design, and the main indicator is the secondary infection risk (SIR) of influenza of close contacts taking Lianhua Qingwen Capsules or placebo within 9 days (±1 day). The test hypotheses are as follows:

H0: π\_T - π\_C ≤ 0

H1: π\_T - π\_C > 0

Note: π\_T and π\_C represent the secondary infection risk (SIR) of influenza within 9 days (±1 day) in the test group and the control group respectively; the lower the SIR, the better.

If there is a significant difference in the SIR of influenza within 9 days (±1 day) between the test group and the control group and the SIR of the test group is smaller than that of the control group, the test group is superior to the control group.

## 9.2 Estimate of sample size

The primary objective of this study is to assess the risk of secondary influenza infection in close contacts of influenza who have taken Lianhua Qingwen Capsules or the placebo within 9 days (±1 day) after randomization. According to the results of previous clinical studies [28,29], the secondary transmission rate of the placebo group is estimated to be 17%, and the experimental group to be 9%; α=0.025, 1-β=0.95, and the sample allocation ratio between the two groups is 1:1; according to the calculation by PASS (2021) software, the test group and the placebo group are expected to each include 527 cases.

The enrollment in this study is based on the results of rapid influenza virus antigen test. Considering the false positive rate of index cases and the false negative rate of close contacts are estimated to be 30% in total, the sample size should be increased to 1,506 cases; plus the drop-out rate of 20%, the sample size should be further increased to 1,884 cases. Therefore, the test group and the placebo group are expected to each include 942 cases.

## 9.3 Analysis population

### 9.3.1 Intent-to-treat set (ITTS)

Including all cases that express their intention to receive treatment, sign an informed consent form, and undergo randomization.

### 9.3.2 Full analysis set (FAS)

Including all cases that have signed informed consent forms and undergone randomization, received treatment, and obtained corresponding efficacy endpoint records. The baseline data analysis and validity analysis are mainly based on the FAS set analysis results. For cases where the entire treatment process is not observed in the FAS set, the last observation data is carried forward to the Last Observation Carry Forward (LOCF). Subjects who withdraw from the study due to the following withdrawal criteria are not included in the FAS analysis as they do not meet the definition of the study population in this study:

1. If an index case is screened as negative by influenza virus nucleic acid test, the clustered unit that this index case belongs to is withdrawn from the study;
2. The close contact is screened as positive by influenza virus nucleic acid test.

### 9.3.3 Per-protocol set (PPS)

A subset of FAS, including all cases in the experiment who complete drug treatment according to the protocol, without significant deviation from the protocol, and complete all evaluation contents. The criteria for the PPS population and their population will be finalized during blind review of data, including at least the following criteria:

① Meet the inclusion criteria specified in the study protocol; fail to meet the exclusion criteria specified in the study protocol;

② Complete all scheduled visits;

③ During the test, no drugs or treatments that may affect the efficacy evaluation are used;

④ Good compliance (80%-120%).

The PPS population is the secondary population for efficacy evaluation in this test. Cases of premature dropout due to ineffectiveness should be included in the per protocol set.

### 9.3.4 Safety set (SS)

Including all cases with recorded safety indicators. The incidence of adverse reactions is based on the total number of SS cases as the denominator.

## 9.4 Statistical analysis

### 9.4.1 General methods

1. Statistical software: SAS9.4 statistical software for statistical analysis.
2. Basic principle: All statistical inferences are made using a bilateral test, with a statistically significant test criterion of 0.05, and a bilateral 95% confidence interval is used for the interval estimation of parameters.
3. Missing data: When the primary effectiveness evaluation indicators are missing, the LOCF method is used to carry forward. Other indicator missing will not be dealt with.
4. Extreme data: Quantitative data are defined as extreme data with an interquartile spacing exceeding P25 (P75) ±3 times. Sensitivity analysis is used when important indicators are involved.
5. Dropout analysis: Summarize the selection and completion status, list the dropout cases, as well as the number of FAS, PPS, and SS population cases. Describe the distribution process of subjects using a flowchart. Evaluate the compliance of the subjects, describe the accompanying diseases and concomitant medication, and list the reasons for the dropout of cases at each time point in each group.
6. Descriptive statistics: The mean, standard deviation and confidence interval are given for the measurement data of normal distribution, and the minimum, maximum, P25, median and P75 are given for the measurement data of non-normal distribution. Pair measurement data, provide the mean, standard deviation, and confidence interval of the difference. When using non-parametric method, give the median and average rank. Provide frequency distribution and corresponding percentages for counting data. For grade data, provide frequency distribution and corresponding percentages, as well as median and average rank.

### 9.4.2 Analysis of primary efficacy endpoints

The primary efficacy endpoint in this study: secondary infection risk (SIR) of influenza within 9 days (±1 day) to close contacts taking Lianhua Qingwen Capsules or the placebo, for which the comparison of difference between groups is conducted by χ2 test or Fisher’s exact test. The 95% confidence interval for the response rate of the two groups is estimated by the Clopper-Pearson exact method, and the 95% confidence interval for the difference of response rate between the two groups (test group - control group) is estimated by the Newcombe method.

### 9.4.3 Analysis of secondary efficacy endpoints

The secondary efficacy endpoints are estimated by t-test, analysis of variance, χ2/Fisher’s exact test or Wilcoxon rank sum test depending on the endpoint properties.

### 9.4.4 Safety analysis

1. AEs and ARs: Lists are made to include all the AEs and ARs. The incidence rates of AEs (ARs) are compared between groups by χ2 test or the Fisher’s exact test.
2. Abnormal changes in laboratory tests: The frequency table of normal and abnormal changes before and after treatment is listed out, and the specific list is made to include abnormal laboratory monitoring indicators changed from normal levels and seriously abnormal laboratory monitoring indicators.
3. The vital signs of each viewpoint are described by mean, standard deviation, number of cases, minimum value and maximum value.

### 9.4.5 Analysis of baseline data

Describe demographic data and other data, symptoms and general conditions. The quantitative data are analyzed by variance or non-parametric statistics according to the distribution of variables. Qualitative data are subjected to χ2 test, Fisher exact probability method, and Wilcoxon rank sum test.

### 9.4.6 Scheduled interim analysis

N/A.

### 9.4.7 Subgroup analysis

1. The preventive efficacy of Lianhua Qingwen Capsules in different virus subtypes is analyzed hierarchically.
2. The preventive efficacy of Lianhua Qingwen Capsules with different treatment protocols on index cases are analyzed hierarchically.

### 9.4.8 Data list for each subject

Data lists of each subject should be listed in the appendix to the statistical analysis report by testing method and time point.

### 9.4.9 Exploratory analysis

N/A.

### 9.4.10 Procedure for modifying deviations from statistical analysis plans

The Statistical Analysis Plan (SAP) is a clear description of the statistical considerations of clinical tests and the intended statistical analysis of data. The first draft of the statistical analysis plan should be developed after the study protocol and case report form are determined. During the clinical test and blind review, SAP can be modified, supplemented and improved, but should be completed and filed before the data is locked. Adjustments to the study protocol, if involved, should also be submitted to the Ethics Committee for review and confirmation.

### 9.4.11 Pharmacoeconomics analysis

Economic evaluation in clinical test involves the following steps: (1) Quantifying the cost and effectiveness of treatment; (2) Evaluating whether there are differences in average cost and effectiveness between treatment groups; (3) Comparing the degree of cost and effectiveness differences, evaluating the cost-effectiveness of treatment, and calculating the Incremental cost -effectiveness ratio, ICER:

In this study, a cost-effectiveness analysis is made based on a societal perspective to evaluate the economics of treatment. Medical and non-medical costs related to diseases, as well as work-related losses caused by diseases, namely indirect costs, are comprehensively considered in the cost from the societal perspective. For effectiveness indicators, the health outcomes of interventions are compared, such as influenza infection rate, hospitalization rate, and severity of infection. In addition, Quality-adjusted Life Years (QALY) integrates survival time and quality, as the most important outcome indicator in economic analysis. The short-term economic impact can be directly observed, while the long-term impact needs to be predicted through decision analysis models.

1. Cost indicators. Cost indicators include direct and indirect costs. Direct costs refer to medical and non-medical expenses directly related to influenza. Direct medical expenses include drug expenses, examination and testing expenses, hospitalization bed expenses, nursing expenses, etc., in addition to information on the treatment costs of adverse reactions and complications. Direct non-medical expenses include transportation, accommodation, and nutritional support expenses and the like for medical treatment. Indirect costs refer to the work-related losses caused by influenza, calculated with the human capital method. The cost data are described by mean, standard deviation, median, and quartile. Depending on the endpoint properties, the comparison between groups is conducted by t-test, analysis of variance, Wilcoxon rank sum test or Kruskall-Wallis test.
2. Effect indicators. The effect indicators include infection rate, probability of mild to moderate disease after infection, probability of severe disease, probability of hospitalization, probability of ICU use, probability of complications, and types and probability of symptoms. χ2 test or Fisher’s exact probability test is used for the comparisons across groups. The utility data in each health state are obtained from published studies on Chinese populations.

# 10. Supporting Documentation and Operational Considerations

## 10.1 Ethical considerations

### 10.1.1 Informed consent process

#### 10.1.1.1 Informed Consent Forms (ICFs) and other documents provided to subjects

The Investigator should provide the subjects with the *Informed Consent Form* during the informed consent process. Before non-clinical routine baseline efficacy evaluation, a written *Informed Consent Form* signed by the subjects and/or legal representatives and witnesses should be obtained.

#### 10.1.1.2 Informed consent process and documentation

The Investigator participating in the clinical trial shall provide details of the clinical trial, including the objective, nature of the trial, possible benefits and risks, alternative treatment methods, and rights and obligations of subjects stipulated in the *Declaration of Helsinki*, so that the subjects have a sufficient understanding and sign the “Informed Consent Form” voluntarily before the clinical trial is conducted. The Investigator shall tell the phone number to each subject who has signed the ICF so that the subjects can contact the Investigator at any time when the disease conditions change during the trial.

Informed consent is a process which begins before an individual agrees to attend the study and continues throughout the study process. The ICFs will be approved by an Institutional Review Board (IRB), and subjects will be asked to read and examine the document. The Investigator will explain the study to the subjects and answer any questions the subjects may raise. The Investigator will verbally explain the study objective, procedure and potential risks, and subjects’ rights to the subjects in a manner that they can understand. Before signing the ICFs, subjects have sufficient time to read it carefully and ask questions. Subjects should have the opportunity to discuss the study with family members or surrogates or to consider for themselves before they agree to participate in the study. Subjects will sign the ICFs prior to any procedure for the study. Subjects shall be informed that their participation in the study is voluntary and may withdraw from the study at any time without prejudice. The Investigator will provide the subjects with copies of the informed consent documents. The informed consent process should be carried out before subjects receive any procedures for the study. The informed consent process (including date) should be documented in source documents, and the signed ICFs should be kept. The Investigator shall specifically inform the subjects that “their quality of medical services will not be adversely affected if they refuse to participate in this study”, to guarantee the rights and welfares of subjects.

If important modifications are made to the study protocol or ICF during the clinical trial, the modified data must be submitted to the Ethics Committee again for approval, and the consent of the subjects must be obtained again.

### 10.1.2 Termination and suspension of study

This study may be temporarily suspended or terminated early if there are sufficient reasonable reasons. The party that will suspend or terminate the study should immediately provide a written notice to the subjects, Investigators, clinical trial institutions and drug regulatory authorities, and record the reasons for the suspension or termination of the study. Where applicable, the Investigator will contact the subjects and notify any change of the scheduled visits.

Conditions that may lead to the termination or suspension of the study include, but are not limited to:

1. Any serious safety problem occurs during the trial.
2. During the trial, the drug is found with too poor or even no efficacy, and it has no clinical value.
3. Any major error is found in the clinical trial protocol during the trial, which makes it difficult to evaluate the drug effect; or, any important deviation is found from a good clinical protocol during its implementation, which makes it difficult to evaluate the drug effect if the trial continues.
4. It is identified that the purpose of the study has been achieved, and the Sponsor or the Investigator believes that there is no need to continue the trial.
5. The Sponsor required discontinuance of the trial (for reasons of funding, management, etc.).
6. The regulatory authorities request the cancellation of the trial.

### 10.1.3 Confidentiality and privacy

Only the investigators and CRA participating in the trial may have access to subjects’ personal medical records, and they will sign the “Investigator’s Statement” including the confidential information. The drug regulatory departments and the Ethics Committee shall have the right to inspect the clinical trial records. The data processing will adopt a “data anonymization” method, and the subject’s individual identity information will be omitted. The medical records of subjects will be kept in the data archives of each clinical trial institution.

The participating investigators, staffs and the sponsor shall keep the subjects’ personal information and privacy rights, including subjects’ clinical information and biological samples used for testing, in strict confidentiality. The study protocol, study-related documents and data and all other information generated during the study are kept strictly confidential. Without the written permission of the Sponsor, no study information or data can be disclosed to an unauthorized third party.

The subjects’ study activities such as informed consent, follow-up observation will be carried out in a quiet and private environment as much as possible.

The CRA, the Sponsor’s authorized representatives, representatives of the Institutional Review Board (IRB), and regulatory agencies may inspect all documents and records that should be kept by the Investigator, including but not limited to the subjects’ medical records and pharmacy records. These records should be allowed to access in each study site.

The subjects’ contact information will be kept in each study site safely for internal use during the study. At the end of the study, all records will be kept in a safe location continuously.

### 10.1.4 Future use of reserved samples and data

Upon consent of the subject and approval of the Ethics Committee, the biological samples collected in this study will be stored in the laboratories of each testing facility. When the testing is completed, samples will be destructed according to the laboratory SOP. At the end of the study, the archived data containing no personal information will be saved in the Sponsor.

### 10.1.5 Medical treatment and protection of subjects

The Investigator of the study site is responsible for the medical treatment of the subjects, make medical decisions related to the clinical trial, and ensure that the subjects receive appropriate treatment when AEs occur during the trial.

The Sponsor and investigators should deal with the SAEs promptly that occur in the trial, take necessary measures to ensure the safety and rights of subjects, and report to them to the drug regulatory department in a timely manner.

The Sponsor shall bear the cost for treatment and economic compensations for the damage or death related to the trial. The Sponsor shall provide legal and economic guarantees to the Investigators (except those caused by medical malpractice).

### 10.1.6 Key roles

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Key Role** | **Organization** | **Contact Person** | **Position/title** | **Contact Address** | **Contact Phone** |
| Principal Investigator | First Affiliated Hospital of Guangzhou Medical University | Zhong Nanshan/Yang Zifeng | Academician/Professor | No.151 Yanjiang West Road, Yuexiu District, Guangzhou | 13622273918 |
| Drug Provider | Shijiazhuang Yiling Pharmaceutical Co., Ltd. | Hou Lili | Deputy Director | Address: No.238 Tianshan Street, High-tech Industrial Development Zone, Shijiazhuang | 18630172387 |

### 10.1.7 Safety supervision

N/A.

## 10.2 Quality assurance and quality control

1. The Sponsor and the testing facility shall establish their respective quality control and quality assurance systems.
2. The Sponsor should confirm that the CRA who has the medical/pharmaceutical background and has received the GCP training is responsible for the monitoring of the clinical trials. The CRA shall participate in the training of the study protocol, conscientiously perform his/her responsibilities, protect the rights and interests of subjects in the clinical trial, ensure the data of the study records and reports are accurate and complete, and the clinical trial complies with the approved protocol, GCP and relevant regulations. The frequency of visits by CRA should meet the need of clinical trial quality control.

### 10.2.1 Matters needing attention for Investigators

1. Investigators participating in the clinical trial should have the expertise, qualifications and abilities for the conduct of clinical trials and the personnel are relatively fixed.
2. Investigators shall receive the training on the clinical trial protocol before the start of clinical trial, so that they have a full understanding of the connotation of all indicators. The description of subjective symptoms should be objective and should not give induction or prompt. The specified objective indicators should be checked according to the time point and method specified in the protocol, and the consistency test should be conducted on the quantitative standards of symptoms and signs.
3. Subjects should receive the return visits according to the time specified in the clinical trial protocol; if the subjects fail to do so, physicians should promptly notify them to receive return visit or follow-up visit.
4. Adverse reactions or unexpected toxic side effects should be observed and tracked. Subjects should be informed of the possible adverse reactions during the trial, and once any adverse reactions occur, they shall notify them to the physicians immediately.
5. Investigators shall sign the Investigator’s Statement.

### 10.2.2 Laboratory quality control

The laboratories of each participating facility shall establish standard operating procedures (SOPs) and quality control procedures for laboratory testing indicators. The test items for each experiment in the participating facility should adopt the national statutory unit of measurement, and the test reports must have complete items (including date, testing items, testing results and their normal reference range), and must be signed by the applying physicians, testing physicians and reviewers.

Before the trial, each participating facility shall submit the laboratory name and the normal reference range of the laboratory indicators to the Sponsor. Any changes in the laboratory, test method, unit of measurement or normal reference range, etc., if any, should be notified to the Sponsor in writing in time, and the effective dates of the changes should be stated, and the applicability of the effective changes to all subjects to be examined should be described. If not, reasons should be given. If there is any change to the laboratories, a copy of the normal reference range of the test items in the new laboratory should be submitted to the Sponsor in time, which should indicate the subjects receiving examination in the new laboratory, and provide the effective date of the new laboratory.

The laboratory technicians participating in the clinical trial should have the expertise, qualifications and abilities for the conduct of clinical trials and the personnel are relatively fixed.

The criteria for judgment of laboratory test abnormality should be based on the normal reference range of each test institution.

### 10.2.3 Monitoring of clinical trials

In order to protect the rights and welfare of subjects and ensure the data are accurate, complete and verifiable, and ensure that the clinical trial complies with the latest approved protocols or protocol amendments, Good Clinical Practice (GCP) and applicable laws and regulations, monitoring should be performed on the testing facility.

1. The detailed requirements for the monitoring of the testing facility will be recorded in the Clinical Monitoring Plan (CMP). The CMP describes who will conduct the monitoring, how often the monitoring will be conducted, the extent of the monitoring, and the distribution of the monitoring reports, etc. Before the start of the study, the project manager works with the quality control department to formulate a monitoring plan according to the project conditions, and complete the clinical trial project monitoring plan. The CRA will arrange the monitoring frequency and monitoring time according to the monitoring plan and actual study progress.
2. The CRA shall submit the monitoring report and monitoring follow-up letter in time after the monitoring visits.

## 10.3 Data processing and record retention

### 10.3.1 Requirements for source data

Source data should be traceable, legible, time-consistent, original, accurate and complete. The sources of source data of this study include but not limited to outpatient medical records, inpatient medical records, laboratory test reports, medical images, subject medication diary cards, subject scoring records, Investigator’s scoring records, adverse event report forms, serious adverse event report forms, drug purchase records, certification copies, etc. See the *Raw Data File Source Table* for details.

### 10.3.2 Data collection and management

In this study, the clinical trial electronic data collection system (EDC), medication diary cards and symptom score form are used. Subjects record the medication status, influenza symptom score, body temperature, etc. through the medication diary card and symptom score form. The Investigator fills out the source document, and the authorized CRC sorts out the medical records and assists the Investigator in inputting the data into the EDC system.

When there is any doubt about the data in the EDC system, the authorized CRC will send an inquiry to the Investigator according to the content of the generated Data Query Form (DQF), and the Investigator should answer and return the Data Query Form as soon as possible. The data administrator will modify, conform and enter the data according to the Investigator’s answers, and when necessary, issue a Data Query Form again.

The medical history, adverse events, and concomitant medication recommendations collected in clinical trials are coded using a standard dictionary. Medical coding should be completed before the database is locked.

After data review and confirmation that the established database is correct, the PI, Sponsor, statisticians and data administrator will lock the data. The locked database generally cannot be unlocked. The unlocking, if required, should be implemented according to the unlocking conditions and process in the SOP, and the unlocking process must be carefully controlled and recorded.

### 10.3.3 Retention of study records

The ownership of all the data and information of this study belongs to the Sponsor; without the written consent of the Sponsor, no one can provide them to a third party, unless required by the drug regulatory department.

Records and data are archived and kept according to the following methods:

The source files are kept by each testing facility according to the relevant regulations on file management, including the confirmation of all participating subjects (different records, such as the original records of the hospital can be effectively checked), all original ICFs signed by the subjects, all case observation forms, detailed drug dispensing records, etc. The Sponsor and the testing facility shall keep the files for 5 years or more after the end of the clinical trial, and the testing facility shall notify the Sponsor before destruction of files.

1. The original medical records of the subjects in the drug clinical trial are kept in the archives of the testing facility of each site.
2. The original reports of laboratory tests and auxiliary tests of subjects are pasted in the original medical records.
3. The case report forms of the clinical trial should be kept in accordance with the *Technical Guidelines for Electronic Data Collection for Clinical Trials*.

### 10.3.4 Blind review

Blind review refers to the blind check and evaluation of the data in the database after the last CRF is entered into the database until the unblinding.

After all the study data have been entered and checked, the data administrator will formulate a data verification report, which includes the checking on the completion of the trial, inspections of inclusion/exclusion criteria, integrity, logic consistency, outlier data, time window, concomitant medications and adverse events, etc.

At the blind review meeting, the PI, Sponsor, CRA, data administrator and biostatistician will review the ICFs signed by subjects, the status of blind maintenance and the emergency unblinding during the trial, etc., and make a decision on the issues raised in the database verification report, and write a blind review report.

The medical history, adverse events, and concomitant medication recommendations collected in clinical trials are coded using a standard dictionary. Medical coding should be completed before the database is locked.

### 10.3.5 Protocol violation

Protocol violation refers to non-compliance with the clinical trial protocol and Good Clinical Practice (GCP). The non-compliance may come from subjects, investigators, or testing facility staffs. Corrective actions shall be taken for the violations and completed in a timely manner.

All protocol violations must be reported for review in accordance with the regulations of the Institutional Review Board (IRB) regulations of each study site. The Investigators are responsible for knowing and complying with the relevant regulations of the IRB.

### 10.3.6 Study publication and data sharing policy

The ownership of all the data and information of this study belongs to the Sponsor; without the written consent of the Sponsor, no one can provide them to a third party, unless required by the drug regulatory department. The study results will be published in the form of literature. Data for this study will not be shared.

### 10.3.7 Policy on conflict of interest

The study should not be influenced by any established or predictable factors (such as pharmaceutical companies). Therefore, any actual conflict of interest with this study will be disclosed and controlled for any person who undertakes the design, conduct, analysis, publication or other aspects of this study, and a statement of conflict of interest will be provided as required. During the design and conduct of the study, persons who may have a conflict of interest will be required to take appropriate measures to control the occurrence of such situations.

## 10.4 Insurance

The Sponsor will apply for insurance coverage for subjects or offer compensations for study-related damages according to regulatory requirements.

## 10.5 of Abbreviations

| **Abbreviation** | **Definition** |
| --- | --- |
| ALT | 丙氨酸氨基转移酶（Alanine aminotransaminase） |
| AST | 天冬氨酸氨基转移酶（Aspartic transaminase） |
| GGT | 谷氨酰转移酶（gamma glutamyl transferase） |
| ALP | 碱性磷酸酶（alkaline phosphatase） |
| ALB | 白蛋白（albumin） |
| CHE | 胆碱酯酶（cholinesterase） |
| TBIL | Total Bilirubin |
| Ccr | Endogenous Creatinine Clearance Rate |
| UREA | Urea |
| BUN | Blood Urea Nitrogen |
| EDC | Electronic Data Capture System |
| eCRF | Electronic Case Report Form |
| GCP | Good Clinical Practice |
| PI | Principal Investigator |
| CRO | Contract Research Organization |
| CRA | Clinical Research Associate |
| CRC | Clinical Research Coordinator |
| ICF | Informed Consent Form |
| AE | Adverse Event |
| SAE | Severity Adverse Event |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| ADR | Adverse Drug Reaction |

## 10.6 Protocol change history

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Date** | **Description of changes** | **Rationale** |
| (N/A) |  |  |  |

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# 12. Appendices

Appendix 1: Packaging Labels of Investigational Drugs

Appendix 2: Influenza Symptom Scoring Criteria

## Appendix 1: Packaging Box Label Format of Investigational Drugs

**Preventive Efficacy of Lianhua Qingwen Capsules on Close Contacts of Seasonal Influenza in a Clustered Environment:**

**A Multicenter, Randomized, Double-blind, Placebo-controlled Study**

Medication for close contacts (for clinical studies only)

Drug No.:

**[Drug name]** Lianhua Qingwen Capsules/ Lianhua Qingwen Capsule Simulator

**[Strength]** 0.35 g/capsule

**[Package]** Aluminum plastic blister package; 12 pills ×2 plates/box, 3 boxes/package

**[Functions and indications]** Lianhua Qingwen Capsules: Clearing plague and detoxifying and releasing lung and expelling heat. It is used for the treatment of influenza with heat-toxicity attacking the lung. The symptoms include fever or high fever, aversion to cold, muscle soreness, nasal congestion and runny nose, cough, headache, dry throat and sore throat, red tongue, yellow or greasy fur, etc. Simulator: No therapeutic effect.

**[Storage]** Preserve under well-sealed conditions in a place unavailable for children, store at a temperature not more than 20℃ and protect from light.

**[Production Batch Number] [Expiry Date] See the primary package**

※Please return the medicine packaging boxes when you return to the hospital※

**First Affiliated Hospital of Guangzhou Medical University**

**Appendix 2: Influenza Symptom Scoring Criteria [30][31][32][33]**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Influenza Symptom** | **Scoring Criteria** | | | |
| **0 (asymptomatic)** | **1 (mild)** | **2 (moderate)** | **3 (severe)** |
| **Fever** | ≤37.2℃ | 37.3～37.9℃ | 38.0～38.9℃ | ≥39℃ |
| **Headache** | Asymptomatic | Occasional headache | Mild to severe | Severe headache, affecting the daily life and work |
| **Sore muscles** | Asymptomatic | Occasional muscle and joint pain | Mild to severe | Severe muscle and joint pain, affecting work and sleep |
| **Aversion to cold** | Asymptomatic | Slight aversion the cold | Aversion to cold, no relief after wearing more clothes | Chills |
| **Runny nose** | Asymptomatic | Occasional runny nose | Mild to severe | Frequent runny nose, affecting work and sleep |
| **Fatigue** | Asymptomatic | Mild fatigue, without affecting daily life and work | Mild to severe | Severe fatigue, affecting the daily life and work |
| **Sore throat** | Asymptomatic | Occasional sore throat | Mild to severe | Severe sore throat, affecting swallowing |
| **Cough** | Asymptomatic | Intermittent cough, without affecting daily life and work | Mild to severe | Frequent coughing day and night, affecting work and sleep |
| **Nasal congestion** | Asymptomatic | Unilateral nasal obstruction | Bilateral nasal obstruction | Bilateral nasal congestion, mouth breathing, affecting sleep |