Informed Consent Information Sheet

Name of the Experiment: Efficacy of Regular ICS/LABA Sequential As-Needed Therapy in Newly Diagnosed Mild Asthma Patients: A Randomized, Parallel, Positive-Control Study

Version 3.0 (May 18, 2023) Research Institution: Shanghai General Hospital Collaborating Institutions: None

We invite you to participate in a trial titled "Efficacy of Regular ICS/LABA Sequential On-Demand Treatment in Newly Diagnosed Mild Asthmatic Patients: A Randomized, Parallel, Positive-Control Study." Before deciding to participate in this trial, please read this informed consent form carefully. If you have any questions or do not understand any part of it, you may ask the researcher responsible for the trial or any member of the trial team to explain any terms or information that are unclear to you.

1. Research Background and Objectives

- **Research Background**

Asthma, or bronchial asthma, is a chronic inflammatory disease of the airways and is currently the second largest respiratory disease in China. Among different severities of asthma, mild asthma accounts for 50%-75%. Some patients with mild asthma have mild or atypical symptoms and relatively normal lung ventilation function, but inflammation of the airways persists. Inadequate treatment can lead to acute attacks and even the risk of death. The preferred treatment regimen for mild asthma is on-demand low-dose inhaled corticosteroids (ICS) combined with rapid-acting long-acting β_2 agonists (LABA). An alternative approach is maintenance therapy with low-dose ICS or other medications, supplemented with as-needed short-acting β_2 agonists (SABA). On-demand use of ICS-formoterol has shown reduced risks of emergency visits and hospitalizations compared to daily maintenance ICS treatment. However, this dosing mode is symptom-based and its effectiveness in controlling airway inflammation needs further exploration. Maintenance therapy with low-dose ICS combined with as-needed SABA effectively reduces asthma symptoms and

related risks of acute attacks, hospitalization, and death. However, compliance with maintenance ICS treatment is poor, leading to increased risk when using SABA alone for acute attacks. Therefore, there is an active need to explore initial treatment strategies for mild asthma.

Based on this background, this study adopts a randomized, parallel, positive-controlled design, enrolling Chinese patients with mild asthma. Participants will be randomized 1:1 to receive either maintenance daily low-dose ICS/LABA combined with as-needed inhalation for 4 weeks (W), compared to initial as-needed low-dose ICS/LABA in mild asthma patients. Following the 4-week period, both groups will continue with as-needed low-dose ICS/LABA treatment. The primary endpoints of the study include improvement rate of forced expiratory volume in 1 second (FEV_1) from baseline at 4 weeks, secondary endpoints include FEV_1 improvement rate from baseline at 24 weeks, markers of asthma exacerbation, and a comprehensive precision assessment based on airway inflammation levels to explore biomarkers that predict the effectiveness of initial maintenance low-dose ICS/LABA treatment in patients with mild asthma. This aims to achieve more precise initial personalized treatment for mild bronchial asthma.

- **Research Objectives**

1) Evaluate the effectiveness of 4 weeks of initial treatment with maintenance combined with as-needed low-dose ICS/LABA compared to initial as-needed low-dose ICS/LABA in patients with mild asthma. Clarify improvements in FEV_1 from baseline, reversibility of airways, and levels of airway inflammation, establishing the best patient population and treatment regimen for drug efficacy.

2) Explore biomarkers that predict the effectiveness of maintenance combined with as-needed low-dose ICS/LABA treatment in patients with mild asthma, based on comprehensive assessment of lung function parameters (FEV_1, FEV1/FVC, PEF, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, MMEF) and levels of airway inflammation.

3) Investigate the impact of initial maintenance combined with as-needed low-dose ICS-formoterol treatment for 4 weeks, followed by as-needed treatment with this medication up to 24 weeks, compared to as-needed treatment up to 24 weeks in the control group. Dynamically monitor clinical indicators to explore the influence on FEV_1 improvement rate

from baseline, symptom improvement, risk indicators for acute attacks, and airway inflammation in mild asthma.

2. Research Methods

- **Eligibility Criteria**

Inclusion Criteria:

- Subjects fully understand the purpose, nature, and methods of the study and voluntarily participate as subjects, signing an informed consent form before any study procedures commence.
- Adults (including males and non-pregnant, non-lactating females) aged 18 to 70 years, meeting the latest Chinese guidelines for the prevention and treatment of asthma, diagnosed for the first time with mild asthma and not in acute exacerbation.
- Objective examination during screening includes any of the following variable airflow limitations: ① Positive bronchodilator test (increase in FEV_1 > 12% and absolute increase in FEV_1 > 200 mL after inhalation of bronchodilator). ② Positive bronchial provocation test; FEV_1 decrease ≥ 20% after inhalation of acetylcholine, indicating a positive result.
- FEV_1 % predicted > 80% on pulmonary function testing.
- Subjects or guardians are able to communicate well with researchers, understand, and comply with all study requirements.

Exclusion Criteria:

- Allergy or intolerance to budesonide, formoterol, salbutamol, or any components of the medication.
- Respiratory tract infection, sinus infection, or otitis media in the 2 months before randomization, causing changes in asthma treatment or expected to change the subject's asthma status according to the investigator's judgment.
- History of chronic obstructive pulmonary disease, interstitial lung disease, restrictive lung disease, pulmonary tuberculosis, cystic fibrosis, bronchiectasis, or alpha-1 antitrypsin

deficiency during screening.

- Major diseases such as congestive heart failure, uncontrolled hypertension, severe coronary artery disease, myocardial infarction, severe arrhythmias, severe hematological, liver disease, neurological, musculoskeletal, endocrine, metabolic, psychiatric, renal disease, or other medical history. If these conditions worsen during the study, participation could endanger the subject or affect the study results.
- Use of short-acting β_2 agonists more than 8 times a day during screening or induction periods.
- Use of beta-blockers during the induction period (including eye drops), oral corticosteroid treatment, systemic steroid treatment, or use of study drugs, leukotriene receptor antagonists (e.g., zafirlukast, pranlukast, montelukast).
- Current smoker with a smoking index > 10 pack-years, or smoking cessation ≤ 6 months before Visit 1 or current smoker.
- Known or suspected alcohol and/or drug abuse, defined as daily average alcohol consumption exceeding 2 units (1 unit = 360 mL beer or 45 mL 40% alcohol, or 150 mL wine).
- Positive pregnancy test or lactating female subjects.
- Use of drugs in the past month that may interact with the study drugs, such as CYP3A4 inhibitors (ketoconazole, itraconazole), cimetidine, disulfiram, metronidazole, or CYP3A4 enzyme inducers (e.g., rifampicin, carbamazepine, phenobarbital).
- Participation in other medical device clinical trials within the past month and/or participation in other drug clinical trials within the past 3 months.
- Asthma symptom score (daytime + nighttime) < 2 points in the week before randomization.
- Inability to comply with study procedures or judged by the investigator as unsuitable for participation in the trial.

3. Study design

1) Experimental Medication

- **Experimental Drug**: Maintenance and as-needed Budesonide/Formoterol Powder Inhaler

(Brand Name: Symbicort 160/4.5®).

- **Positive Control Drug**: As-needed Budesonide/Formoterol Powder Inhaler (Brand Name: Symbicort 160/4.5®).
- **Emergency Medication**: Salbutamol Inhalation Aerosol (Brand Name: Ventolin®), used only in emergencies after exceeding the maximum dose of as-needed low-dose ICS-Formoterol.

2) Enrollment and Study Procedure

Before screening, researchers must obtain informed consent from participants, collect information, and conduct the following assessments:

- **Demographic Information**: Collecting data on allergies, medical and treatment history, smoking and alcohol use, clinical trial history.
- **Eligibility Criteria**: Confirm inclusion/exclusion criteria.
- **Physical Examination**: Conduct a physical exam.
- **Diagnostic Tests**: 12-lead ECG, blood routine test, chest CT, induced sputum, pulmonary function tests, bronchial dilation or provocation tests.
- **Training**: Training on oral inhalation medication, mobile pulmonary function testing, and peak flow meter use.
- **Medication Records**: Record concurrent medications and adverse events.

For eligible participants:

- **Observation Period**: Treatment and efficacy observation period (D1–D168)
    - **Study Group**: budesonide 160 μg-formoterol 4.5 μg (Symbicort 160/4.5) ®），administered as one inhalation twice daily for maintenance for 4 weeks, sequential as-needed therapy for symptom relief to 24-week (no more than 8 inhalations per day) (168 days).
    - **Control Group**: Inhaled budesonide-formoterol as needed when symptoms are present (Symbicort 160/4.5) ®），no more than 8 inhalations per day, continuous

to 24-week (168 days).

Allowed Concurrent Medications:

- **As-needed Salbutamol Inhalation Aerosol**: Daily maximum of 8 puffs (100μg/puff).
- **Nasal Corticosteroids**: Topical hydrocortisone preparations (≤1% hydrocortisone ointment) and corticosteroid-containing creams.
- **Antihistamines**: Short- and long-acting antihistamines (e.g., loratadine, azelastine, desloratadine, terfenadine) for allergic symptoms other than asthma. Antihistamine eye drops are also allowed.
- **Cold Medications**: Note that antipyretics and analgesics may exacerbate asthma. Mucolytics and cough suppressants without bronchodilators or anti-inflammatory drugs are permitted. Any other medication that does not affect the trial, as determined by the investigator.

Prohibited Concurrent Medications:

- **Other β2-Agonists**: Long- or short-acting β2-agonists, except for emergency use of salbutamol.
- **Sympathomimetics**: Various medications such as imipramine, diphenhydramine, chlorpromazine, cimetidine, disulfiram, and metronidazole.
- **CYP3A4 Inhibitors**: Ketoconazole, fluconazole, etc.
- **Inhaled Corticosteroids**: Other than the study drug.
- **Leukotriene Receptor Antagonists**.
- **Xanthines**: Theophylline or sustained-release formulations (e.g., aminophylline, theophylline, doxofylline, dyphylline).
- **Anticholinergics**: For example, ipratropium bromide, oxitropium bromide, tiotropium bromide.
- **Mast Cell Stabilizers**: Ketotifen, nedocromil sodium, cromolyn sodium.
- **CYP3A4 Inducers**: Rifampin, carbamazepine, phenytoin, dexamethasone, phenobarbital.

- **Anti-IgE Therapy**.
- **Traditional Chinese Medicine or Chinese Patent Medicines**: For treating asthma or other allergic conditions (e.g., Suhuang Zhike Capsules).
- **Combination Products**: Containing xanthines or ephedrine (e.g., compound methoxamine capsules, Meixin Pseudoephedrine Solution).
- **Other Medications**: As determined by the investigator that may affect the trial.

All use of concurrent medications must be recorded in detail.

Follow-up Schedule:

- **Day 29±3**: Measurement of vital signs; physical examination; laboratory tests: blood routine, urine routine, blood biochemistry; induced sputum; pulmonary function tests; ACT score; collection of diary cards, remaining medication, and packaging; adherence assessment; recording of concurrent medications and adverse events.
- **Regular Follow-ups**: At weeks 8, 12, 16, and 20.
    - Record concurrent medications, adverse events, acute exacerbations, symptom control days, symptom scores, and mobile pulmonary function data.
- **Day 168±3**:
    - **Bronchial Dilation Test**: FeNO; induced sputum; laboratory tests: asthma acute exacerbation-related indicators, asthma symptom control weeks, ICS and OCS usage doses, and background medication usage.

3) Statistical Analysis

Sample Size:

- The study plans to include 90 subjects, randomized into 2 groups with 45 subjects each. Using superiority analysis, assuming α is one-sided 0.025, β is 0.2, with reference to previous studies and pilot results, the study group is expected to have a mean of 290 mL, the control group a mean of 105 mL, and a standard deviation of 279 mL for the difference in the main efficacy indicators between the study and control groups. Therefore, each group needs to

enroll 37 subjects, with a dropout rate of 20%, requiring 45 subjects per group, totaling 90 subjects.

Statistical Analysis:

- In addition to the superiority test for the primary endpoint (overall significance level of one-sided 0.05), unless otherwise specified, all statistical tests are two-sided with a significance level of 0.05. Descriptive statistics for continuous variables include counts, means, standard deviations, medians, quartiles, minimum, and maximum values. Categorical variables are described using frequencies and percentages.

4. Research Risks and Benefits

1) Research Risks

- Lung function tests, chest CT scans, blood tests, induced sputum tests, and other examinations are routine diagnostic and therapeutic procedures that do not increase additional risks. However, every effort will be made to minimize related risks.

2) Research Benefits

- Participants will receive standardized diagnosis and treatment for asthma and comprehensive disease management.

5. Your Rights

- You have the right to decide whether to participate in this study. If you cannot decide immediately, you have sufficient time to consider. You may consult with trusted relatives, friends, etc., before making a decision. Declining to participate will not affect your relationship with the researchers or sponsors, nor will it result in discrimination or retaliation against you. Your treatment and rights will not be affected. If you decide to participate, we hope you can complete the trial without special reasons. However, you have the right to withdraw from the trial at any time. Please inform the researchers promptly if you decide to withdraw.

- **During the trial, you can always access information related to you in this study.**

6. Privacy Protection

The personal information you provide to the researcher (such as name, gender, contact information, survey questionnaire, etc.) may be disclosed to the following individuals or organizations, besides the normal research needs:

- Personnel associated with the research funding institution related to this trial (inspectors, auditors, etc.).
- Administrative agencies such as the National and Local Food and Drug Administration.

However, no one may disclose your personal information to others or other organizations without your permission. Apart from the researcher and administrative agencies, no other individuals or entities have the right to initiate contact with you regarding this study or provide you with information related to this study.

The results of this study may be published in the form of academic papers, but your personal information will not appear in any publicly published documents.

7. Others

1) Funding Sources:
    - Special Research Project Fund of Shanghai First People's Hospital
    - China International Medical Exchange Foundation Fund
2) Free Examination Items Include:
    - Experimental drug: Xīnbìkědūbǎo 160/4.5®
    - Free examinations: Initial treatment at 4 weeks and follow-up examinations at 24 weeks, including pulmonary function tests, FENO detection, complete blood count, induced sputum examination.
3) The researcher may withdraw you from this trial without your consent under the following circumstances for your health:
    - Continuing participation may result in risks outweighing benefits.
    - Failure to follow the researcher's instructions and the study protocol.
    - Early termination of the study.
4) (We still recommend that you take necessary contraceptive measures during the trial. If you or your spouse becomes pregnant during the study, please inform the researcher or your doctor immediately.) If applicable, please fill out; if not, please delete.

5) Two copies of this informed consent form will be prepared, with one copy retained by the researcher and one by you.

8. Compensation for Harm Caused by the Study

If any harm directly arises from your participation in this trial, you will not be responsible for any medical expenses incurred for treatment. These expenses will be borne by the researcher.

9. Contact Information

1) Office of the Medical Ethics Committee, Shanghai First People's Hospital Contact: 021-36126254
2) Researcher's Name: Zhou Yan Contact: 18964705743

Consent Form

Participant Consent Statement:

1. I have carefully read the Participant Information Sheet and understand the background of this trial. The researcher has provided detailed explanations about the nature of the study and potential adverse reactions, and has addressed my questions.
2. I understand that my decision to participate in this trial is voluntary after fully considering the contents of the Participant Information Sheet. I am aware that my treatment and rights will not be affected if I choose not to participate.
3. I agree to follow the researcher's instructions and participate in the trial according to the study protocol. I reserve the right to withdraw from the trial at any time, and I will promptly inform the researcher before withdrawing.
4. During the trial, I will promptly inform the researcher of any discomfort or symptoms.

Participant's Signature:

Name (Printed in block letters): _____

Signature: _____

Date of Signature: _____

Researcher's Signature: _____

Name (in block letters): _____

Signature: _____

Date of Signature: _____

Proxy/Guardian Signature (if applicable): _____

Reason why subject cannot sign this page: _____

Relationship of proxy/guardian to subject: _____

Signature (in block letters): _____

Signature: _____

Date of Signature: _____