Shanghai General Hospital

Clinical research projects initiated by researchers

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Clinical Study Protocol Abstract

Study Title	Efficacy of Regular ICS/LABA Sequential As-Needed Therapy in Newly Diagnosed Mild Asthma Patients: A Randomized, Parallel, Positive-Control Study
Study Overview	Bronchial asthma (referred to as asthma) is a chronic inflammatory disease of the airways and has become the second largest respiratory disease in China. Among different severity levels of asthma, mild asthma accounts for 50%-75%. Some patients with mild asthma have mild symptoms and atypical presentations, and their pulmonary function is relatively normal. However, airway inflammation still exists, and without sufficient treatment, there remains a risk of acute attacks or even death. The preferred treatment pathway for mild asthma is as-needed low-dose inhaled corticosteroids (ICS) combined with fast-acting long-acting β_2 agonists (LABA). An alternative pathway involves maintenance treatment with low-dose ICS or other medications, supplemented by as-needed short-acting β_2 agonists (SABA). Compared to daily maintenance ICS therapy, as-needed ICS-LABA therapy, such as ICS-formoterol, reduces the risk of emergency visits and hospitalizations. However, this dosing mode is symptom-driven and may not adequately control airway inflammation, particularly in newly diagnosed patients. Our early studies have shown that initiating maintenance therapy with low-dose ICS-formoterol as-needed can alleviate symptoms and improve lung function, establishing a habit of maintenance treatment. Therefore, initiating 4 weeks of combined maintenance and as-needed therapy aims to achieve better improvement in inflammation and lung function, helping patients identify their optimal health level for subsequent self-management of as-needed treatment.

	Based on this premise, this study employs a randomized, parallel, positive-controlled design to enroll patients with newly diagnosed mild asthma. Participants will be randomized 1:1 to receive either as-needed low-dose ICS-formoterol supplemented with initial 4-week maintenance therapy or as-needed low-dose ICS-formoterol alone until Week 24, comparing the efficacy in mild asthma patients. Study endpoints include the improvement rate of forced expiratory volume in one second (FEV_1) after 4 weeks of maintenance treatment compared to baseline, and secondary endpoints include FEV_1 improvement rate at 24 weeks compared to baseline, asthma exacerbation-related indicators at 4 and 24 weeks, symptom improvement, and inflammation control. The study also explores biomarkers that can effectively predict the efficacy of initial maintenance therapy with low-dose ICS-formoterol in mild asthma patients, aiming to achieve more personalized initial treatment for mild asthma.	
Study Objective and Endpoints	**Study Objective**	**Study endpoints**
	Primary Objective	**Primary Endpoint**
	• To assess the effectiveness of initiating 4 weeks of combined maintenance and as-needed low-dose ICS-formoterol versus as-needed low-dose ICS-formoterol alone in newly diagnosed patients with mild asthma. Specifically, the study aims to determine the improvement in forced expiratory volume in one second (FEV_1), a marker	• The change in FEV_1 from baseline at week 4.

	of airflow limitation, after 4 weeks of treatment compared to baseline.	
	Secondary Objective	**Secondary Endpoints**
	• Evaluate the improvement in symptoms, small airway function, and airway inflammation after 4 weeks of combined maintenance and as-needed low-dose ICS-formoterol treatment, establishing the optimal patient population and treatment regimen for drug efficacy. • Compare the dynamic monitoring of clinical indicators between 4 weeks of combined maintenance and as-needed low-dose ICS-formoterol treatment followed by as-needed therapy up to week 24 versus initial as-needed therapy up to week 24. Specifically, assess the impact on acute exacerbations, improvement in lung function compared to baseline, symptom relief, and airway inflammation from 1 to 24 weeks.	• Assessment of symptom improvement (ACT and ACQ scores), changes in small airway function, improvement in airway inflammation levels (eosinophils, Fractional Exhaled Nitric Oxide (FENO), induced sputum cell count, and inflammation markers), and incidence of acute exacerbations at Week 4. • Evaluation from Weeks 1 to 24 of improvement rates in FEV_1 and small airway function compared to baseline, improvement in symptoms (ACT and ACQ scores), frequency of asthma exacerbations, time to first asthma exacerbation, instances of hospitalization (including intubation and ICU admission) or emergency room visits (not resulting in hospitalization), weeks of asthma symptom control, doses of ICS and oral

		corticosteroids (OCS) used, and improvement in airway inflammation (FENO, eosinophils, induced sputum cell count, and inflammation markers).
	Exploratory Objective	**Exploratory Endpoints**
	• Using comprehensive lung function parameters (FEV_1, FEV_1/FVC, PEF, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, MMEF) and levels of airway inflammation, explore population characteristics and biomarkers that effectively predict the efficacy of maintenance low-dose ICS-formoterol treatment in patients with mild asthma.	• Stratify the study based on the presence of baseline small airway dysfunction and conduct a layered investigation using comprehensive lung function parameters and levels of airway inflammation. This exploration aims to identify characteristics and biomarkers that determine the suitability of initial use of maintenance low-dose ICS/LABA therapy in patients with mild asthma.
Study Design	Randomized, Parallel, Positive-Control Study	
Study Cohort	Chinese patients with newly diagnosed mild bronchial asthma	
Sample size	90 cases	
Inclusion criteria	The eligible subjects for this study must meet all of the following criteria: 1. Subjects must fully understand the purpose and procedures of the study, voluntarily agree to participate as a subject, and sign an informed consent form before any study procedures commence.	

	2. Adults (including males and non-pregnant, non-lactating females) aged 18 to 70 years (inclusive of borderline values), diagnosed for the first time with mild asthma according to the GINA and latest domestic guidelines for the prevention and treatment of bronchial asthma, and not in an acute exacerbation period. 3. During screening, meet any of the following objective criteria for variable airflow limitation: - Positive bronchodilator response (increase in FEV_1 >12% and >200 mL absolute increase in FEV_1 after inhalation of bronchodilator). - Positive bronchial provocation test; FEV_1 decrease ≥20% after inhalation of acetylcholine provocation agent. 4. During screening and at the D-1 visit of the run-in period, have a predicted FEV_1% of >80% in pulmonary function testing. 5. Subjects or their guardians are capable of good communication with the researcher, understanding, and adhering to all study requirements.
Exclusion criteria	Subjects who meet any of the following criteria are not eligible for inclusion in this study: 1. Allergy or intolerance to budesonide, formoterol, salbutamol, or any components of these medications. 2. Respiratory tract infections, sinus infections, or otitis media requiring changes in asthma treatment within 2 months prior to randomization, or anticipated to change the subject's asthma status based on the investigator's judgment. 3. History of chronic obstructive pulmonary disease, interstitial lung disease, restrictive lung disease, pulmonary tuberculosis, cystic

	fibrosis, bronchiectasis, or alpha-1 antitrypsin deficiency during screening. 4. Presence of major illnesses such as congestive heart failure, uncontrolled hypertension, severe coronary artery disease, myocardial infarction, severe arrhythmias, severe hematologic, liver, neurological, musculoskeletal, endocrine, metabolic, psychiatric, renal disease, or other significant medical history. Conditions that, if worsened during the study, could pose a risk to the patient by participating in the study or affect study results. 5. During screening and the D-1 visit of the run-in period, having used short-acting beta-agonists (SABA) more than 8 times in one day. 6. Use of beta-blockers (including eye drops) during the run-in period, oral corticosteroid treatment, systemic steroid treatment, treatment with study drugs, or use of leukotriene receptor antagonists (such as zafirlukast, pranlukast, montelukast, etc.). 7. History of smoking with a smoking index >10 pack-years. 8. Quitting smoking ≤6 months before screening visit (Visit 1) or current smoker. 9. Known or suspected alcohol and/or drug abuse; alcohol abuse defined as consuming more than 2 units of alcohol daily (1 unit = 360 mL of beer, 45 mL of 40% alcohol liquor, or 150 mL of wine). 10. Abnormal clinically significant results in vital signs, physical examination, 12-lead electrocardiogram, chest CT, complete blood count, urinalysis, blood biochemistry, coagulation function, etc., during screening and the D-1 visit of the run-in period, except those judged by the investigator to be unrelated to the study disease and associated conditions and do not affect the enrollment of subjects. 11. Positive pregnancy test or lactating female subjects. 12. Use of medications within 1 month prior to screening that may interact with the study drug, such as CYP3A4 inhibitors (ketoconazole, itraconazole), cimetidine, disulfiram, metronidazole, or CYP3A4 enzyme strong inducers (rifampicin, carbamazepine, phenytoin, etc.).

	13. Participation in other medical device clinical trials within 1 month prior to screening and/or participation in other drug clinical trials within 3 months prior to screening. 14. Asthma total symptom score (daytime + nighttime) <2 points in the week prior to randomization. 15. Inability to comply with study procedures or deemed unsuitable for study participation by the investigator.
Treatment Groups	• **Treatment Plan for the First 4 Weeks:** **Study Group (Maintenance at initial treatment sequential as-needed therapy group):** Participants will inhale budesonide-formoterol (Symbicort 160/4.5®) twice daily, morning and evening, 1 inhalation each time, totaling 2 inhalations per day, continuously for 4 weeks. If symptoms such as wheezing, shortness of breath, with or without chest tightness or cough persist during this maintenance phase, participants may additionally use budesonide-formoterol on an as-needed basis, up to a total daily dose not exceeding 8 inhalations. **Control Group (As-needed therapy group):** Participants will use budesonide-formoterol (Symbicort 160/4.5®) on an as-needed basis, up to a maximum of 8 inhalations per day, continuously for 4 weeks. Participants should record the number of uses and times in their diary cards after each use. • **Week 5 to Week 24:** **1. Study Group (Maintenance at initial treatment sequential as-needed therapy group):** Participants will continue to use budesonide-formoterol (Symbicort 160/4.5®) on an as-needed basis, up to a maximum of 8 inhalations per day, from Week 5 to Week 24, after receiving maintenance + as-needed low-dose ICS/LABA treatment for the initial 4 weeks. **2. Control Group (As-needed therapy group):** Participants will continue to use budesonide-formoterol (Symbicort 160/4.5®) on an

	as-needed basis, up to a maximum of 8 inhalations per day, from Week 5 to Week 24. Participants should continue recording the number of uses and times in their diary cards after each use.
Study Completion Criteria	The study and control groups will follow the treatment plan for 4 weeks, and complete pulmonary function tests, blood routine tests, FENO (Fractional Exhaled Nitric Oxide) measurement, and induced sputum examination at the end of 4 weeks. Follow-up visits according to the protocol will continue until week 24, when pulmonary function tests, blood routine tests, FENO measurement, and induced sputum examination will be completed again.
Study Withdrawal Criteria	The criteria and procedures for subject withdrawal from the study are as follows: **Researcher-initiated early withdrawal:** The researcher may decide to withdraw a subject from the study if it is deemed medically necessary from an ethics perspective, if there is a serious adverse event (SAE) that makes it inappropriate to continue participation, if a serious other concurrent illness arises that is judged by the researcher to be in the subject's best interest to withdraw, if additional clinical asthma medications (excluding those allowed by the protocol) are required during the study period, if there is poor compliance by the subject (e.g., non-adherence to medication and scheduled assessments, irregular diary card entries, use of other medications or foods affecting safety evaluations and study outcomes), if the subject becomes pregnant, if concomitant medications that may affect outcome assessments are used, or if the researcher determines other reasons unsuitable for continued participation in the study. **Subject-initiated withdrawal:** Subjects have the right to withdraw from the study at any time. Reasons for subject-initiated withdrawal include voluntary withdrawal by the subject or loss to follow-up. For subjects who withdraw from the study, the researcher should inquire about the reasons for withdrawal, document them, and attempt

	to conduct exit safety assessments whenever possible. Reasons may include intolerance to adverse reactions, inability to continue participating in the clinical study due to other reasons, or loss to follow-up without explanation. And try to ensure that the subjects complete the exit safety inspection as much as possible.
Study Termination Criteria	Reasons for premature study termination may include but are not limited to the following: 1.The study drugs are found to be ineffective or lack clinical value in the treatment regimen outlined by the study protocol. 2.Significant errors or serious deviations are discovered in the clinical research protocol during implementation, making it difficult to evaluate the drug's effects.
Dropout Criteria	Setting a dropout rate of 20% according to the sample size.
Data analysis and statistical methods	Differences between groups were determined using differential test methods. For quantitative data, paired t-tests or Wilcoxon rank-sum tests were used for analysis. For qualitative data, χ^2 tests or Fisher's exact probability tests were employed for analysis. Non-parametric tests were used for inter-group or intra-group comparisons of ordinal data before and after treatment.
Research units	Shanghai General Hospital
The duration of the study	From March 31, 2024, to March 30, 2027.

1. Research Background

Bronchial asthma (asthma) is a chronic inflammatory airway disease characterized by recurrent episodes of wheezing, shortness of breath, with or without chest tightness or coughing. It is associated with airway hyperresponsiveness and variable airflow limitation, and has become the second largest respiratory disease in China. Approximately 45.7 million adults in China suffer from asthma [1], with mild asthma accounting for 50%-75% of all asthma cases [2].

Mild asthma is defined differently at initial diagnosis and during follow-up. At initial diagnosis, it is based on non-acute symptoms and pulmonary function test results [3]: (1) symptoms < once daily; (2) may affect activity and sleep; (3) nocturnal asthma symptoms < once weekly; (4) forced expiratory volume in the first second (FEV_1) ≥ 80% predicted, or peak expiratory flow (PEF) ≥ 80% personal best, with PEF variability < 30%. For follow-up or treated patients, classification follows the Global Initiative for Asthma (GINA) guidelines [4], which assess if control is achieved with Step 1 or 2 treatment.

Current issues in the treatment of mild bronchial asthma: Some patients with mild asthma have mild or atypical symptoms, relatively normal lung function, but still exhibit airway inflammation. Inadequate treatment may lead to acute exacerbations or even death. Nearly one-third of asthma deaths occur in patients with mild asthma [5], attributed to inadequate appreciation of the benefits of long-term anti-inflammatory therapy, treatment focus on symptom relief, and issues such as poor treatment adherence and lack of self-management. Due to these factors and the potential progression to moderate to severe asthma, GINA 2022 emphasizes the risk of severe exacerbations and the necessity of inhaled corticosteroid (ICS) therapy when using the term "mild asthma" [6].

Current strategies for initial treatment of mild bronchial asthma and recognition of acute exacerbations: Treatment strategies for mild asthma include preferred and alternative pathways. The preferred pathway involves as-needed low-dose ICS combined with a rapid-acting long-acting β_2-agonist (LABA). The alternative pathway includes maintenance treatment with low-dose ICS or other medications, with as-needed short-acting β_2-agonists (SABA) [7].

Recognition of acute exacerbations in mild asthma: Even in cases of mild asthma, monitoring of symptoms to detect changes in disease status is essential. Signs indicating poor control or impending acute exacerbation include: daytime asthma symptoms, nocturnal awakening due to asthma, significantly limited activities due to asthma, increased use of reliever medications; asthma control test (ACT) scores < 19; PEF < 80% personal best; elevated fractional exhaled nitric oxide (FeNO), blood eosinophils, and total serum IgE compared to baseline [8]. These are critical indicators that should be closely monitored in clinical research.

Why emphasize the early use of ICS-containing medications from diagnosis? Compared to using SABA alone, as-needed low-dose ICS-formoterol can reduce the risk of severe exacerbations and emergency visits or hospitalizations by 65% [9]. This anti-inflammatory relief strategy significantly reduces severe exacerbations, regardless of baseline symptom frequency, lung function, history of exacerbations, or inflammatory phenotype (T2-high or T2-low) [10, 11]. Early initiation of low-dose ICS treatment in asthma patients improves lung function to a greater extent compared to starting ICS 2-4 years later [12, 13]. Failure to start ICS early leads to higher required doses later and poorer lung function [14]. Patients not using ICS and experiencing severe exacerbations show more pronounced long-term decline in lung function compared to ICS users [15]. Early initiation of ICS treatment in occupational asthma significantly relieves symptoms, improves lung function, and reduces airway hyperresponsiveness [16]. Therefore, initial asthma treatment should commence with ICS-containing medications at the time of diagnosis (or shortly thereafter).

Why is there still a need to optimize initial treatment strategies for mild bronchial asthma?

- In adults and adolescents with mild asthma, as-needed low-dose ICS-formoterol compared to SABA alone [10, 11] reduces the risk of severe exacerbations, emergency visits, or hospitalizations by approximately two-thirds. As-needed ICS-formoterol compared to daily ICS maintenance therapy reduces the risk of emergency visits and hospitalizations, with no clinically important difference in symptom control. However, this as-needed dosing model is based solely on symptom control, and the extent of airway inflammation control in newly diagnosed patients using as-needed medication warrants further exploration.

- Maintenance therapy with low-dose ICS combined with as-needed SABA [17-20] effectively alleviates asthma symptoms and reduces the risk of exacerbations, hospitalizations, and mortality. However, poor adherence to ICS in clinical practice increases the risk of exacerbations when patients use SABA alone. As-needed use of ICS-SABA may be an option for mild asthma, but data is limited to small-scale studies.

- Early initiation of maintenance therapy with low-dose ICS-formoterol at initial diagnosis improves symptom relief and enhances lung function more effectively [21].

FEV_1, or forced expiratory volume in one second, is an objective indicator of the degree of airflow limitation. Improvements in FEV_1 reduce the risk of future exacerbations and are positively correlated with symptom control. FEV_1 serves as an objective assessment to evaluate the early effectiveness of medications [4].

Therefore, this clinical study hypothesizes whether starting daily maintenance therapy with low-dose ICS-formoterol at the onset of mild asthma treatment, followed by as-needed therapy, can achieve better control of mild asthma by promoting sufficient anti-inflammatory treatment to attain a relative plateau in lung function. Hence, this study employs a randomized, parallel, positive-control design with a 1:1 random allocation. It focuses on newly diagnosed mild asthma patients, divided into: 1) initial treatment with 4 weeks of maintenance and as-needed low-dose ICS-formoterol therapy, followed by as-needed treatment with the same medication up to 24 weeks; 2) as-needed low-dose ICS-formoterol therapy up to 24 weeks. The study aims to clarify FEV_1 improvement after 4 weeks of maintenance therapy with low-dose ICS-formoterol and to assess airway reversibility, symptom improvement, and inflammation control post bronchodilator testing. Based on comprehensive and precise evaluation of airway inflammation levels, the study aims to explore biomarkers that can effectively predict the efficacy of low-dose ICS-formoterol maintenance therapy in patients with mild asthma. Initial maintenance therapy with low-dose ICS-formoterol for 4 weeks, followed by as-needed therapy up to 24 weeks, while the control group receives only as-needed treatment, serves as the positive control. The study will evaluate FEV_1 improvement rates from baseline, asthma

symptom control, acute exacerbations, and other outcomes during the 24-week follow-up to achieve more personalized treatment of mild asthma.

References

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2. Study Objectives and Endpoints

2.1 Primary Study Objectives

2.1.1 Evaluate the efficacy of initiating treatment with 4 weeks of maintenance combined with as-needed low-dose ICS-formoterol compared to as-needed low-dose ICS-formoterol alone in patients with mild asthma at initial diagnosis. Determine improvements in FEV_1 compared to baseline after 4 weeks of treatment, and improvements in airway reversibility and inflammation levels, to establish the optimal patient population and treatment regimen.

2.1.2 Explore biomarkers that effectively predict the efficacy of sequential maintenance as-needed low-dose ICS-formoterol treatment in patients with mild asthma based on comprehensive evaluation of lung function parameters (FEV_1, FEV_1/FVC, PEF, $FE_{F25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, MMEF) and airway inflammation levels.

2.1.3 Initiate treatment with 4 weeks of maintenance combined with as-needed low-dose ICS-formoterol, followed by as-needed treatment with the same medication up to 24 weeks, compared to as-needed treatment alone up to 24 weeks. Dynamically monitor clinical indicators to explore the impact of early maintenance low-dose ICS-formoterol treatment on risk indicators for acute exacerbations, improvement rates in FEV_1 from baseline, symptom improvement, and airway inflammation in mild asthma.

2.2 Study Endpoints / Observational Indicators

2.2.1 Primary Study Endpoints / Major Observational Indicators: Change in FEV_1 from baseline before bronchodilator use at week 4.

2.2.2 Secondary Study Endpoints / Secondary Observational Indicators:

(1) Observations after 4 weeks of treatment regarding symptom improvement, small airway function, airway inflammation, and acute exacerbations:

1）Change in ACT and ACQ questionnaire scores from baseline after 4 weeks of treatment; change in mean daytime and nighttime asthma symptom scores from baseline after 4 weeks of treatment;

2）Change in lung function tests FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ values from baseline after 4 weeks of treatment; changes in average morning and evening weekly PEF values from baseline after 4 weeks of treatment; weekly PEF variability during treatment; reversibility improvement after bronchodilator use;

3）Airway inflammation: Improvement in FENO, eosinophil count, induced sputum cell classification counts, and inflammation markers after 4 weeks of treatment;

4）Number of asthma exacerbations after 4 weeks of treatment, time to first exacerbation, number of exacerbations requiring hospitalization (including ICU admission) or emergency room visits (not resulting in hospitalization), weeks of asthma symptom control, doses of ICS and OCS used, and background medication use.

(2) Observations after 24 weeks of treatment regarding large airway function FEV_1, small airway function, symptom improvement, airway inflammation, and acute exacerbations:

1）Change in FEV_1 from baseline after 24 weeks of treatment;

2）Change in lung function tests FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ values from baseline after 24 weeks of treatment; changes in average morning and evening weekly PEF values from baseline after 24 weeks of treatment; weekly PEF variability during treatment;

3）Change in ACT and ACQ questionnaire scores from baseline after 24 weeks of treatment; change in mean daytime and nighttime asthma symptom scores from baseline after 24 weeks of treatment;

4）Peripheral blood eosinophils (absolute and relative values), IgE, FeNO, CaNO, cytokines (IL-4, IL-5, IL-13, etc.), and induced sputum inflammation levels after 24 weeks of treatment;

5）Number of subjects experiencing asthma exacerbations; number of asthma exacerbations, weeks of asthma symptom control, use of rescue medication, doses of ICS and OCS used, and background medication use after 24 weeks of treatment.

Exploratory Endpoints / Exploratory Observational Indicators:

Stratification and correlation analysis based on the presence of baseline small airway dysfunction and comprehensive lung function parameters (FEV_1, FEV_1/FVC, PEF, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, MMEF), peripheral blood eosinophils (absolute and relative values), IgE, FeNO, and other parameters. Comparison of the predictive capabilities of these parameters for treatment outcomes.

This exploratory analysis aims to:

1) Evaluate whether baseline small airway dysfunction affects treatment response in patients with mild asthma.

2) Assess the correlation between baseline lung function parameters, peripheral blood eosinophils, IgE levels, FeNO levels, and treatment efficacy.

3) Investigate the predictive value of these parameters in determining the response to sequential maintenance and as-needed low-dose ICS-formoterol treatment in patients with mild asthma.

The analysis will help identify potential biomarkers that could predict treatment response and guide personalized asthma management strategies.

3. Research Methods

3.1 Study Design

This study employs a randomized, parallel-group, positive-control design.

3.2 Sample Size

For the primary efficacy endpoint, which is the change in FEV1 from baseline after 4 weeks of treatment (positive increase), a superiority test will be conducted. The study will calculate a one-sided 97.5% confidence interval for the difference in means

between the study and control groups. If the lower limit of the confidence interval is greater than 0 mL, superiority will be established. Based on references from SYGMA1 and SYGMA2 studies, as well as preliminary studies, the study assumes a mean change of 290 mL in the study group and 105 mL in the control group, with a standard deviation of 279 mL (References: O'Byrne PM, et al. N Engl J Med. 2018;378(20):1865-76; Beasley R, et al. N Engl J Med. 2019;380:2020-2030).

The study employs a superiority analysis with a one-sided α of 0.025 and β of 0.2. Based on previous research and pilot study results using t-tests, each group requires 37 subjects. Accounting for a 20% dropout rate, each group will enroll 45 subjects, totaling 90 subjects to be randomized into two groups, with 45 subjects each in the study and control groups.

3.3 Randomization and Blinding

Randomization is conducted using a central randomization system. During screening, subjects are identified using screening numbers, which are three-digit Arabic numerals (e.g., 001). A non-blinded statistician utilizes SAS 9.4 or higher statistical software to generate a randomization list in blocks of 1:1. The blinded allocation is then imported into the central randomization system. After screening qualification, researchers log into the system to input subject information and obtain a randomization number. The randomization number is visible to the randomization administrator and the patient but blinded to the evaluator (a professional independent from the clinical physician).

3.4 Study Population

The study includes adults (males and non-pregnant, non-lactating females) aged 18 to 70 years, including the boundary values. Participants are newly diagnosed with mild asthma according to the "Guidelines for the Prevention and Treatment of Bronchial Asthma" (2020 edition) and GINA guidelines (2024 edition).**3.4.1 Inclusion Criteria**

Patients must meet all of the following criteria to be eligible for inclusion in the study:

1) Informed Consent: Subjects must fully understand the purpose, nature, and methods of the study, voluntarily agree to participate as subjects, and sign an informed consent form before any study procedures begin.

2) Adults: Including males and non-pregnant, non-lactating females aged 18 to 70 years, including boundary values. Patients must be newly diagnosed with mild asthma according to the latest domestic guidelines for the prevention and treatment of bronchial asthma and should not be in an acute exacerbation period.

3) Objective Confirmation of Variable Airflow Limitation during Screening: Positive bronchodilator test (increase in FEV_1 >12% and absolute increase >200 mL after inhalation of bronchodilator; or PEF ≥20%).

Positive bronchial provocation test (FEV_1 decrease ≥20% after inhalation of acetylcholine provocation agent).

4) Lung Function Criteria: FEV_1 % predicted >80% at screening and Day -1 visit.

5) Communication and Compliance: Subjects or guardians must be able to communicate well with the investigator, understand, and comply with all study requirements.

3.4.2 Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1) Allergy or Intolerance: Known allergy or intolerance to budesonide, formoterol, salbutamol, or any components of the study medications.

2) Respiratory Infections: Occurrence of respiratory tract infection, sinusitis, or otitis media within 2 months prior to randomization, which led to changes in asthma treatment or is anticipated by the investigator to affect the subject's asthma status.

3) Medical History: History of chronic obstructive pulmonary disease (COPD), interstitial lung disease, restrictive lung disease, pulmonary tuberculosis, cystic fibrosis, bronchiectasis, or alpha-1 antitrypsin deficiency at screening.

4) Significant Diseases: Presence of significant diseases such as congestive heart failure, uncontrolled hypertension, severe coronary artery disease, myocardial infarction, severe arrhythmias, severe hematological, liver, neurological, musculoskeletal, endocrine, metabolic, psychiatric, renal diseases, or other conditions

deemed by the investigator to pose a risk to the patient's participation in the study or influence study results if worsened during the study.

5) Excessive Short-Acting Beta-Agonist (SABA) Use: History of using SABA more than 8 times per day for one day during screening.

6) Medication Use: Use of beta-blockers (including eye drops), oral glucocorticoids, systemic steroid treatment, study drug treatment, leukotriene receptor antagonists (such as zafirlukast, pranlukast, montelukast), within the induction period.

7) Smoking: Past history of smoking with a smoking index >10 pack-years.

8) Smoking Cessation: Smoking cessation ≤6 months before screening visit (Visit 1) or current smoker.

9) Alcohol and Substance Abuse: Known or suspected alcohol and/or drug abuse, defined as daily average alcohol consumption exceeding 2 units (1 unit = 360 mL of beer, 45 mL of 40% alcohol, or 150 mL of wine).

10) Clinical Laboratory Abnormalities: Clinically significant abnormalities in vital signs, physical examination, 12-lead electrocardiogram, chest CT, blood routine (elevated blood eosinophils), CRP, urine routine, blood biochemistry, coagulation function, etc., at screening and Day -1 visit, unless judged by the investigator to be unrelated to the study disease and associated conditions and not affecting subject enrollment.

11) Pregnancy and Lactation: Positive pregnancy test or lactating female subjects.

12) Medication Interactions: Use of medications within 1 month prior to screening that may interact with the study drugs, such as CYP3A4 inhibitors (ketoconazole, itraconazole), cimetidine, disulfiram, metronidazole, or CYP3A4 enzyme inducers (rifampicin, carbamazepine, phenytoin).

13) Participation in Other Trials: Participation in other medical device clinical trials within 1 month before screening or other drug clinical trials within 3 months before screening.

14) Asthma Symptoms: Total asthma symptom score (daytime + nighttime) <2 points in the week before randomization.

15) Non-compliance or Unsuitability: Inability to comply with study procedures or deemed unsuitable for the study by the investigator.

4. Treatment Regimen/Interventions

4.1 Study Medication (ICS/LABA)

Investigational Drug: Budesonide-Formoterol powder for inhalation (brand name: Symbicort Turbuhaler 160/4.5®).

Positive Control Drug (ICS/LABA): Budesonide-Formoterol powder for inhalation (brand name: Symbicort Turbuhaler 160/4.5®).

4.2 Dosage Regimen

Week 1-4 Treatment Regimen:

Study Group (Maintenance + As-Needed Sequential Treatment Group):

Inhalation of Budesonide-Formoterol (Symbicort Turbuhaler 160/4.5®) twice daily (morning and evening), 1 inhalation each time, total of 2 inhalations per day for 4 weeks.

If symptoms such as wheezing, shortness of breath, with or without chest tightness or cough persist during this maintenance treatment phase, the study drug can be used as-needed in addition to daily regular use, not exceeding a total of 8 inhalations per day.

Control Group (As-Needed Treatment Group):

Inhalation of Budesonide-Formoterol (Symbicort Turbuhaler 160/4.5®) as needed, not exceeding 8 inhalations per day for 4 weeks.

The number of inhalations and times of use should be recorded in the subject's diary card.

Week 5-24 Divided into:

Study Group:

After initial maintenance + as-needed low-dose ICS/LABA treatment for 4 weeks, switch to as-needed treatment with the same medication until week 24.

Control Group:

Continuation of as-needed low-dose ICS/LABA treatment until week 24.

Emergency Medications (Rescue Medications):

Albuterol (Salbutamol) Inhaler: Inhalation of albuterol aerosol inhaler (brand name: Ventolin®) as needed during acute exacerbations, not exceeding 8 puffs per day, 100 μg per puff.

Usage details such as number of puffs, frequency, and time should be recorded in the subject's diary card.

4.3 Permitted and Prohibited Concomitant Medications/Treatments

Permitted Medications/Treatments:

1) As-needed albuterol (salbutamol) inhaler (up to 8 puffs per day, 100 μg/puff).

2) Intranasal corticosteroids: Subjects may receive intranasal corticosteroids to control symptoms of allergic diseases.

3) Topical corticosteroids: Subjects may use topical corticosteroid preparations (≤1% hydrocortisone ointment) for skin diseases; use of creams containing corticosteroids is allowed.

4) Antihistamines: Short-acting and long-acting antihistamines (such as loratadine, cetirizine, desloratadine, fexofenadine) for the treatment of allergic symptoms (excluding asthma). Additionally, the use of antihistamine eye drops is allowed during the study.

5) Cold medications: Caution should be taken with antipyretic analgesics that may exacerbate asthma.

6) Expectorants and cough suppressants without bronchodilators or anti-inflammatory drugs.

7) Other medications as judged by the investigator not to affect the study.

Prohibited Medications/Treatments:

1) Other long-acting or short-acting β2-adrenergic receptor agonists except for rescue medication salbutamol.

2) Sympathomimetic drugs.

3) Promethazine, diphenhydramine, chlorpromazine, cimetidine, disulfiram, metronidazole.

4) Inhibitors of cytochrome P450 subfamily CYP3A4 (ketoconazole, fluconazole, etc.).

5) Inhaled corticosteroids, except for study medications.

6) Leukotriene receptor antagonists.

7) Theophylline or sustained-release theophylline preparations (e.g., aminophylline, theophylline, doxofylline, dyphylline).

8) Anticholinergic drugs (e.g., ipratropium bromide, oxitropium bromide, tiotropium bromide).

9) Mast cell stabilizers (e.g., ketotifen, nedocromil sodium, cromoglicic acid).

10) CYP3A4 enzyme strong inducers such as rifampicin, carbamazepine, phenobarbital, dexamethasone, phenytoin.

11) Anti-IgE antibody therapy.

12) Traditional Chinese medicine or proprietary Chinese medicine for asthma and other allergic diseases (e.g., Su Huang Zhi Ke Capsule).

13) Compound preparations containing theophylline or ephedrine alkaloids (e.g., compound methoxyphenamine capsules, pseudoephedrine solution).

14) Other medications judged by the investigator to affect the study.

All concomitant medication details must be recorded in detail. The investigator should record specific information regarding the subject's concomitant medications in the

original medical record, including the name of the medication, dosage, route of administration, frequency, dose, start date, and end date.

5. Study Procedures

5.1 Study Duration

The study duration is approximately 24 weeks, including screening period, run-in period, treatment and efficacy observation period.

5.2 Screening Period (D-8~D-4) - Visit 1

Informed Consent: Obtain informed consent from subjects before screening.

Information and Examination:

1) Collect demographic information.
2) Gather allergy history, medical history/treatment history, smoking and alcohol history, clinical research history.
3) Confirm inclusion/exclusion criteria.
4) Physical examination.
5) Blood routine test.
6) IgE levels.
7) Chest CT scan.
8) Pulmonary function tests.
9) Bronchodilator or provocation tests.
10) Induced sputum examination.
11) Training on inhalation of study medications.
12) Record concomitant medications.
13) Record adverse events.

Eligible subjects receive albuterol inhaler for run-in period use and diary card.

5.3 Run-in Period (D-3~D-1)

Subjects use albuterol inhaler as needed, not exceeding 8 puffs per day, 100 μg per puff.

Record the number of puffs used, frequency, and time in the diary card.

5.4 Visit 2 (D-1)

Eligible subjects return to the hospital for:

1) Vital signs measurement.

2) Daytime and nighttime symptom scoring.

3) ACQ5 questionnaire.

4) ACT questionnaire.

Evaluate subjects for study group assignment based on assessments.

Confirm inclusion/exclusion criteria.

Manage symptomatic outpatient treatment for screen failures.

Randomization into two groups:

1) Study Group: Inhalation of Budesonide-Formoterol (Symbicort Turbuhaler 160/4.5®) twice daily (morning and evening), 1 inhalation each time, not exceeding 8 inhalations per day, for 4 weeks. As-needed use allowed if necessary.

2) Control Group: As-needed inhalation of Budesonide-Formoterol (Symbicort Turbuhaler 160/4.5®), not exceeding 8 inhalations per day, for 4 weeks.

Dispense study medications (Budesonide-Formoterol powder inhaler, albuterol inhaler), diary cards, peak flow meter.

Instruct daily morning and evening PEF (peak expiratory flow) measurements.

Instruct recording of daytime and nighttime asthma symptom scores in the diary card.

Enter into the initial 4-week treatment and efficacy observation period.

5.5 Week 1-4 Treatment and Efficacy Observation Period (D1~D28)

- Subjects inhale study medications daily at home.

1) Study Group: Inhalation of Budesonide-Formoterol (Symbicort Turbuhaler 160/4.5®) twice daily, not exceeding 8 inhalations per day if as-needed treatment is required.

2) Control Group: As-needed inhalation of Budesonide-Formoterol (Symbicort Turbuhaler 160/4.5®), not exceeding 8 inhalations per day.

- Record medication usage frequency and times in the diary card.
- PEF measurements.
- Record daytime and nighttime asthma symptom scores.
- Record concomitant medications.
- Record adverse events.

5.6 Visit 3 (D28±3d, i.e., 4 weeks ± 3 days)

- Vital signs measurement.
- Physical examination.
- Laboratory tests: Blood routine test, pulmonary function tests, induced sputum.
- ACQ assessment.
- ACT assessment.
- Collect diary cards, remaining medications and packaging for compliance assessment.
- Record concomitant medications.
- Record adverse events.
- Adjust subsequent medication administration:

1) Study Group: As-needed inhalation of Budesonide-Formoterol, not exceeding 8 inhalations per day, for 4 weeks.

2) Control Group: As-needed inhalation of Budesonide-Formoterol, not exceeding 8 inhalations per day, for 4 weeks.

Provide diary cards and schedule mobile pulmonary function and FeNO tests at 8, 12, 16, 20 weeks.

5.7 Week 5-24 Treatment and Efficacy Observation Period (D29~D168)

1) Subjects inhale study medications daily at home.

2) Both Study and Control Groups: As-needed inhalation of Budesonide-Formoterol, not exceeding 8 inhalations per day.

3) Record medication usage frequency and times in the diary card.

4) PEF measurements.

5) Record daytime and nighttime asthma symptom scores.

6) Record concomitant medications.

7) Record adverse events.

5.8 Visit 4, 5, 6, 7 at Week 8 (DAY56), 12 (DAY84), 16 (DAY112), 20 (DAY140)

1) Monitor full parameters of mobile pulmonary function and FeNO at each visit.

2) Record concomitant medications.

3) Record adverse events.

4) Record acute exacerbations.

5) Record weeks of asthma symptom control.

6) ACT symptom score.

7) Collect diary cards, remaining medications and packaging for compliance assessment.

5.9 Exit Visit at Week 24 (D168±3 days)

1) Full pulmonary function test + bronchodilator test.
2) FeNO.
3) Blood routine test.
4) Induced sputum examination.
5) Markers of asthma exacerbation.
6) Weeks of asthma symptom control.
7) Record concomitant medications.
8) Record adverse events.
9) Record acute exacerbations.
10) Record ICS and OCS usage doses and background medication usage.
11) ACT symptom score.
12) Collect diary cards, remaining medications and packaging for compliance assessment.

5.10 Study Discontinuation/Early Withdrawal

Follow-up procedures for subjects who discontinue or withdraw early:

1) Vital signs measurement.
2) Physical examination.
3) Laboratory tests: Blood routine test, full pulmonary function test + bronchodilator test, FeNO, induced sputum.
4) ACQ assessment.
5) ACT assessment.
6) Markers of asthma exacerbation.

7) Weeks of asthma symptom control.

8) Record concomitant medications.

9) Record adverse events.

10) Record acute exacerbations.

11) Record ICS and OCS usage doses and background medication usage.

12) Collect diary cards, remaining medications and packaging for compliance assessment.

5.11 Medication Compliance

Use diary cards to record ACT and ACQ5 symptom scores.

Use Langye APP for dynamic follow-up and monitoring of medication compliance.

Real-time statistical analysis of medication usage frequency.

This outline provides a comprehensive overview of the study procedures, ensuring adherence to protocol and thorough documentation of all relevant data throughout the 24-week study duration.

6. Study Evaluation

Primary Efficacy Endpoints

1) Change in FEV1 (Forced Expiratory Volume in 1 second) from baseline after 4 weeks of treatment with bronchodilator therapy.

Secondary Efficacy Endpoints

1) Change in FEV1 from baseline after 24 weeks of treatment.
2) Change in Asthma Control Test (ACT) questionnaire score from baseline after 4-24 weeks of treatment.
3) Change in pulmonary function tests (FVC, FEV_1/FVC, $FEF_{25\%-75\%}$) from baseline after 4-24 weeks of treatment.
4) Improvement in FENO (Fractional exhaled Nitric Oxide), eosinophils, induced sputum cell counts, and inflammatory markers at 4 and 24 weeks of treatment.
5) Number of asthma exacerbations from 1-24 weeks of treatment.

6) Amount of rescue medication use from 1-24 weeks.

7) Number of weeks with asthma symptom control from 1-24 weeks.

Exploratory Research

- Stratified study based on parameters such as large and small airway dysfunction, comprehensive lung function parameters (FEV_1, FEV_1/FVC, PEF, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, MMEF), peripheral blood eosinophils (absolute and relative values), FeNO, etc., to identify optimal treatment groups.

Safety Evaluation Endpoints

- Summarize incidence, frequency, and occurrence rates of adverse events (AEs), treatment-emergent adverse events (TEAEs), and drug-related TEAEs by formulation group, severity, System Organ Class (SOC), and Preferred Term (PT).
- Calculate the incidence rate of adverse events statistically, considering each SOC and PT per subject up to once.

7. Exiting or Terminating the Study

Participant Withdrawal

Researcher-Initiated Withdrawal: Participants may be withdrawn from the study by the researcher in the following circumstances:

1) Ethical Considerations: The researcher determines it necessary to stop the trial from a medical ethics perspective.

2) Serious Adverse Event (SAE): The participant experiences an SAE that makes continued participation inappropriate.

3) Serious Other Concurrent Illness: The participant develops a severe concurrent illness that, in the researcher's judgment, makes withdrawal from the study in the participant's best interest.

4) Acute Exacerbation: The participant experiences an acute exacerbation during the study period that warrants withdrawal from the trial.

5) Need for Other Clinical Asthma Medication: During the study, the participant requires clinical asthma medication not allowed by the protocol.

6) Poor Compliance: Poor compliance with the study protocol (e.g., non-compliance with medication or assessments, inadequate diary card records, use of other medications affecting safety evaluation or trial results).

7) Pregnancy: The participant becomes pregnant during the study.

8) Other Reasons Deemed Unsuitable: The researcher determines other reasons that make continued participation in the study unsuitable for the participant.

Participant-Initiated Withdrawal: Participants have the right to withdraw from the study at any time for reasons including:

1) Voluntary Withdrawal: The participant voluntarily decides to withdraw from the study.

2) Lost to Follow-up: The participant becomes lost to follow-up for reasons such as inability to continue clinical research or unexplained absence.

For participants who withdraw from the study, the researcher should inquire about the reasons for withdrawal, document and track these reasons (e.g., intolerable adverse reactions, inability to continue clinical research due to other reasons, or unexplained loss to follow-up), and attempt to complete safety assessments upon withdrawal if feasible.

Study Termination Criteria

The study may be terminated prematurely for reasons including but not limited to:

1) Inadequate Treatment Effect: The study drug treatment shows poor or ineffective clinical outcomes, lacking clinical value.

2) Major Protocol Deviations or Serious Bias: Significant errors or serious deviations occur in the clinical study protocol implementation, making it difficult to evaluate drug effects.

8. Dropout Criteria: 20% Dropout Rate

A dropout rate of up to 20% is anticipated in this study. Participants may discontinue their participation voluntarily or at the discretion of the researcher due to various reasons outlined in the protocol.

9. Adverse Events

An adverse event (AE) refers to any untoward medical occurrence in a participant who has received study drug(s), including symptoms, signs, diseases, or laboratory findings, regardless of whether they are related to the investigational drug.

10. Statistical Analysis

Statistical analyses will be conducted with a significance level of 0.05 for two-sided tests, unless otherwise specified. Descriptive statistics for continuous variables will include counts, means, standard deviations, medians, quartiles, minimum, and maximum values. Categorical variables will be described using frequencies and percentages.

11. Data Management

The data collection and management system for this project is the Deppi Electronic Data Capture (EDC) System.

- eCRF Design: The eCRF is designed based on the protocol and includes all specified data points except for external data.
- Database Establishment: A database is constructed with logic check rules configured, system functionalities set up, and permissions managed by system administrators based on user roles.
- Database Testing: Testing involves data entry, export, logic checks, eCRF interface usability, and system functionality.
- Data Collection: Researchers access the data management system independently to collect study data.
- Data Verification: Medical and statistical personnel collaborate in data verification.

12. Quality Control

- eCRF and Original Records: The eCRF is not the original document; all data entered in the Case Report Form (CRF) must trace back to original records in electronic or participant files.

1) During the Study: Checks include completeness, consistency, and accuracy of eCRF entries; confirmation of original data; quality control of eCRF entries; progress of participant enrollment; compliance with the study protocol and Good Clinical Practice (GCP); and proper storage, distribution, and inventory of study drugs.

2) Data Preservation: Researchers must retain original records for every participant, including demographics, medical information, laboratory data, ECG results, and any other assessments. Participant identity information in original records must remain confidential.

3) eCRF Verification: Researchers enter data into the eCRF, while statisticians verify and address any data queries.

- Quality Control (QC): Before initiating clinical research, researchers receive protocol training. Quality control personnel verify basic conditions to ensure compliance with study requirements. Throughout the study, researchers adhere to institutional Standard Operating Procedures (SOPs) and study protocols, maintaining accurate, timely, complete, and standardized records. At study completion, the research unit organizes and archives relevant project documents.

- Quality Assurance (QA): Researchers establish their own quality assurance systems, fulfill their responsibilities, strictly follow the clinical research protocol, and implement appropriate Standard Operating Procedures (SOPs) to ensure the quality control and implementation of quality assurance systems in clinical research.

Researchers and clinical research institutions have direct access to source data and source documents related to the clinical study.

14. Ethics Protection and Informed Consent for Clinical Research

Ethical considerations relevant to this study are addressed, including the need for informed consent from participants.

15. Appendix

An appendix can include diagnostic criteria for important indicators relevant to the study.

This comprehensive outline covers the essential aspects of data management, quality control, statistical analysis, adverse events, dropout criteria, and ethical considerations pertinent to conducting the clinical research study effectively and ethically.