

Clinical Study Protocol with Amendment 01

A Randomized, Blinded, Parallel Group, Placebo-Controlled, Multiple Dose, Multicenter, Multinational Study to Compare the Therapeutic Equivalence of a Budesonide 80 mcg/Formoterol Fumarate Dihydrate 4.5 mcg Inhalation Aerosol (manufactured by [REDACTED] for Watson Laboratories Inc.) to Symbicort® (Budesonide 80 mcg/Formoterol Fumarate Dihydrate 4.5 mcg Inhalation Aerosol) (manufactured by AstraZeneca) in Adolescent and Adult Patients with Asthma

Study Number ACT-2015-075-0AA

NCT02495168

Protocol with Amendment 01 Approval Date: 24 February 2017

PROTOCOL TITLE

A Randomized, Blinded, Parallel Group, Placebo-Controlled, Multiple Dose, Multicenter, Multinational Study to Compare the Therapeutic Equivalence of a Budesonide 80 mcg/Formoterol Fumarate Dihydrate 4.5 mcg Inhalation Aerosol (manufactured by Catalent for Watson Laboratories Inc.) to Symbicort® (Budesonide 80 mcg/Formoterol Fumarate Dihydrate 4.5 mcg Inhalation Aerosol) (manufactured by AstraZeneca) in Adolescent and Adult Patients with Asthma

Sponsor: Watson Laboratories Inc.
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054, USA

Sponsor Representative: [REDACTED]

Clinical Research Organization: [REDACTED]

Medical Monitor: [REDACTED]

Sponsor Protocol No.: ACT-2015-075-0AA

Study Drug Name: Budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg inhalation aerosol pressurized metered dose inhaler (pMDI) manufactured by [REDACTED] for Watson Laboratories Inc.

Development Phase: III

Date/Version of Protocol: 22 April 2016, Version 1 (Final)

Date/Version of Protocol Amendment: 20 January 2017, Version 2 (Amendment 1.0)

Date/Version of Protocol Amendment: 24 February 2017, Version 3 (Amendment 1.0)

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, the Code of Federal Regulations, and with other applicable regulatory requirements.

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SPONSOR SIGNATURE PAGE

Declaration of Sponsor

Title: A Randomized, Blinded, Parallel Group, Placebo-Controlled, Multiple Dose, Multicenter, Multinational Study to Compare the Therapeutic Equivalence of a Budesonide 80 mcg/Formoterol Fumarate Dihydrate 4.5 mcg Inhalation Aerosol (manufactured by ██████████ for Watson Laboratories Inc.) to Symbicort® (Budesonide 80 mcg/Formoterol Fumarate Dihydrate 4.5 mcg Inhalation Aerosol) (manufactured by AstraZeneca) in Adolescent and Adult Patients with Asthma

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and all amendments, the guidelines on Good Clinical Practice, and the Code of Federal Regulations.

██████████
████████████████████
████████████████████
████████████████████

Date

Declaration of the Investigator and/or Principal/Global Investigator

Title: A Randomized, Blinded, Parallel Group, Placebo-Controlled, Multiple Dose, Multicenter, Multinational Study to Compare the Therapeutic Equivalence of a Budesonide 80 mcg/Formoterol Fumarate Dihydrate 4.5 mcg Inhalation Aerosol (manufactured by ██████████ for Watson Laboratories Inc.) to Symbicort[®] (Budesonide 80 mcg/Formoterol Fumarate Dihydrate 4.5 mcg Inhalation Aerosol) (manufactured by AstraZeneca) in Adolescent and Adult Patients with Asthma

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic CRF (eCRF), and other scientific data.

The study will be performed according to the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and all amendments, the guidelines on Good Clinical Practice, and the Code of Federal Regulations.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Investigator

Signature

Date

Name (block letters)

Title (block letters)

Institution (block letters)

Phone number

PROTOCOL SYNOPSIS

Title	A randomized, blinded parallel group, placebo-controlled, multiple dose, multicenter, multinational study to compare the therapeutic equivalence of a budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg inhalation aerosol (manufactured by [REDACTED] for Watson Laboratories Inc.) to Symbicort® (budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg inhalation aerosol) (manufactured by AstraZeneca) in adolescent and adult patients with asthma.
Sponsor Study No.	ACT-2015-075-0AA
Phase	III
Study Drug Name:	Generic budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg (BDS 80/FFD 4.5) inhalation aerosol pressurized metered dose inhaler (pMDI).
Sponsor	Watson Laboratories Inc. Morris Corporate Center III 400 Interpace Parkway Parsippany, NJ 07054, USA
Sponsor Representative	[REDACTED]
Medical Monitor	[REDACTED]
Study Centers	Up to 110 sites in the United States (US). Sites in Europe may be considered in case recruitment is lower than expected in US sites.
Objectives	The objective of this pivotal trial is to confirm the therapeutic equivalence of a new generic fixed-dose combination product containing BDS 80/FFD 4.5 (per actuation) inhalation aerosol pMDI manufactured by [REDACTED] for Watson Laboratories Inc. and reference listed drug (RLD) Symbicort® (budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg inhalation aerosol) manufactured by AstraZeneca, in adolescent patients and adult patients with chronic but stable asthma as defined in National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPP 3) guidelines. To ensure adequate study sensitivity the test and RLD products should both be statistically superior to placebo ($p < 0.05$) with regard to the bioequivalence study primary endpoints.
Design	This is a randomized, blinded, multiple dose, placebo-controlled, parallel group design consisting of a 2-week open placebo Run-in Period followed by a 6-week randomized Treatment Period with either test product (new generic fixed-dose combination product containing

BDS 80/FFD 4.5 inhalation aerosol; manufactured by [REDACTED] for Watson Laboratories Inc.) or RLD Symbicort® (manufactured by AstraZeneca), or placebo (manufactured by [REDACTED] for Watson Laboratories Inc.).

This study is designed in accordance with the recommendations outlined in the US Food and Drug Administration (FDA) Draft Guidance on Budesonide; Formoterol fumarate dihydrate (June 2015).

Treatment

Run-in Period:

Placebo: Generic pMDI containing placebo aerosol for inhalation (open label).

Route: Oral inhalation.

Posology: Two inhalations twice daily, with a dosing interval of approximately 12 hours.

Duration: 14 days (up to 21 days).

Treatment Period:

Randomized study drug:

Test: Generic budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg (BDS 80/FFD 4.5) inhalation aerosol pMDI, manufactured by [REDACTED] for Watson Laboratories Inc.

Reference: Symbicort® (budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg inhalation aerosol, manufactured by AstraZeneca) [REDACTED]

Placebo: Generic pMDI containing placebo to match generic test product, aerosol for inhalation [REDACTED].

Dose Regimen (all study drugs):

Route: Oral inhalation.

Posology: Two inhalations twice daily (such that the cumulative single dose is budesonide 160 mcg/formoterol fumarate dihydrate 9 mcg twice daily), with a dosing interval of approximately 12 hours. Last dose on the morning of Visit 4.

Duration: 42 days (up to 49 days).

Number of Patients

Approximately 1130 patients will be randomized [REDACTED]

Population

Male and non-pregnant female patients (≥ 12 and ≤ 75 years of age) with asthma as defined by the NAEPP 3 guidelines.

Inclusion criteria:

1. Adolescent and adult male or female patients (≥ 12 and ≤ 75 years of age).
2. Female patients must not be lactating or pregnant at screening, as documented by a negative serum pregnancy test with a minimum

- sensitivity of 25 IU/L or equivalent units of beta-human chorionic gonadotropin (β -hCG) at screening.
3. Women of childbearing potential (WOCBP) and female partners (WOCBP) of male patients participating in the study, must commit to consistent and correct use of an acceptable method of birth control (at the Investigator's discretion) throughout the study and for 30 days after study drug discontinuation.
 4. Male patients and male partners of female patients (WOCBP) must commit to consistent and correct use of an acceptable method of birth control (at the Investigator's discretion) throughout the study and for 30 days after the study drug discontinuation.
 5. Diagnosed with asthma as defined by the NAEPP 3 at least 6 months prior to screening. If the patient is new to the study site, the Investigator must confirm the patient's asthma diagnosis. Acceptable means include either medical records or pharmacy records.
 6. Moderate to severe asthma with a pre-bronchodilator FEV₁ of $\geq 45\%$ and $\leq 85\%$ of the predicted normal value during measured at least 6 hours after short-acting β agonist (SABA) and at least 24 hours after the last dose of long-acting β agonist (LABA) at the screening visit (Visit 1) and on the first day of treatment (prior to randomization at Visit 2).
 7. Currently non-smoking, negative for urine cotinine at screening, having not used tobacco products (i.e., cigarettes, cigars, pipe tobacco, electronic cigarettes) within the past year, and had ≤ 10 pack-years of historical use.
 8. Body mass index (BMI) between 18 and 40, inclusive, for patients ≥ 18 years old. For adolescent patients 12 to 17 years old, BMI between 15 and 40 inclusive (in accordance with the BMI range typical for the age).
 9. $\geq 15\%$ and ≥ 0.20 L reversibility of FEV₁ within 30 minutes following 360 mcg (4 puffs) of albuterol (400 mcg salbutamol) inhalation (pMDI). If the patient achieves $< 15\%$, but $\geq 10\%$ reversibility at Visit 1, the site may instruct the patient to hold LABA and/or inhaled corticosteroids (ICS) and return up to 7 days later for a repeat test. Only 1 repeat of the Visit 1 spirometry (to retest reversibility) is allowed per screening.
 10. Able to perform valid and reproducible spirometry per American Thoracic Society/European Respiratory Society (ATS/ERS) standards at screening.
 11. Able to inhale study drug properly.
 12. Willing to discontinue asthma medications (ICS and LABAs) during the Run-in Period and for the remainder of the study.
 13. Able to replace current regularly scheduled SABAs with albuterol/salbutamol inhaler for use only on as needed basis for the duration of the study (patients should be able to withhold all

- inhaled SABAs for at least 6 hours prior to lung function assessments on study visits).
14. Able to continue the following medications without a significant adjustment of dosage, formulation, dosing interval for the duration of the study, and judged able by the Investigator to withhold them for the specified minimum time intervals prior to each clinic visit, if applicable:
 - Short-acting forms of theophylline: 12 hours.
 - Twice-a-day controlled-release forms of theophylline: 24 hours.
 - Once-a-day controlled-release forms of theophylline: 36 hours.
 15. Able to discontinue the following medications for the specified minimum time intervals prior to the Run-in Period and for the remainder of the study, if applicable:
 - Oral corticosteroids for 30 days.
 - Parenteral corticosteroids for 30 days.
 - Oral (not inhaled) SABAs for 24 hours.
 16. Clinical laboratory tests (clinical chemistry, hematology, and urinalysis) and 12-lead electrocardiogram (ECG) conducted at the screening visit within normal limits or abnormal but not clinically significant to the Investigator. The QTc should be calculated using Bazett's formula.
 17. Willing to give written informed consent/assent, and willing and able to follow the study rules and procedures.
 18. Stable on chronic asthma treatment regimen for at least 4 weeks prior to enrollment.
 19. Ability to perform forced expiratory assessments according to ATS standards.

Randomization eligibility criteria:

1. Baseline pre bronchodilator FEV₁ should be $\geq 45\%$ and $\leq 85\%$ of predicted normal value and not vary by more than $\pm 20\%$ from the screening visit FEV₁ value.
2. Compliance during the Run-in Period of at least 75% based on eDiary entries is required for a patient to qualify for randomization. Compliance with the run-in placebo treatment must be between 75% and 125%.
3. Documented total asthma symptom score of ≥ 1 for at least 2 days during the Run-in Period.

Exclusion criteria:

1. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnea, respiratory arrest or hypoxic seizures, asthma-related syncopal episode(s), or hospitalizations within the past year or during the

Run-in Period.

2. Exercise-induced asthma as the only asthma-related diagnosis.
3. Evidence or history of clinically significant disease or abnormality including congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, or cardiac dysrhythmia. In addition, historical or current evidence of significant hematologic, hepatic, neurologic, psychiatric, renal, or other diseases that, in the opinion of the Investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbated during the study. Patients with well-controlled hypertension, diabetes or hypercholesterolemia are not excluded as long as their medication does not interfere with the study.
4. Any other clinically significant pulmonary disease except for asthma, including chronic obstructive pulmonary disease (COPD), interstitial lung disease, cystic fibrosis, bronchiectasis, chronic bronchitis, emphysema, active pulmonary tuberculosis, pulmonary carcinoma, pulmonary fibrosis, or pulmonary hypertension. In addition, obstructive sleep apnea warranting a prescription for continuous or biphasic positive airway pressure (CPAP or BiPAP).
5. Patients who required systemic corticosteroids (for any reason) within the past 4 weeks.
6. Patients with hypersensitivity to any sympathomimetic drug (e.g., formoterol, albuterol/salbutamol, or salmeterol) or any inhaled, intranasal, or systemic corticosteroid therapy.
7. Patients taking medication(s) (either daily or as needed) with the potential to affect the course of asthma or to interact with sympathomimetic amines, e.g.,:
 - Oral β -blockers.
 - Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir).
 - Monoclonal antibodies/Biologic agents which may affect the course of asthma (such as mepolizumab, reslizumab, lebrikizumab, and others).
8. Viral or bacterial, upper or lower respiratory tract infection or sinus or middle ear infection within 2 weeks prior to the screening visit or during the Run-in Period.
9. Factors (e.g., infirmity, disability or geographic location) that the Investigator feels would likely limit the patient's compliance with the study protocol or scheduled clinic visits.
10. Anti-IgE (such as omalizumab) within the 6 months prior to screening.
11. History of alcohol or drug abuse within the last 6 months.
12. A positive urine drug screen at Visit 1. Exceptions are made for a positive urine drug screen at Visit 1 for opiates or stimulants if there is a documented prescription with supporting medical history

and diagnosis, and the Principal Investigator assesses there are no safety concerns with patient participation. Screened patients with a urine drug screen positive for Marijuana/Tetrahydrocannabinol are not eligible for study participation, without exceptions. Repeat drug screening is not allowed.

13. Have received any investigational treatment within 30 days (or within 5 terminal half-lives of the investigational drug whichever is longer) of the screening visit or plans to receive investigational treatment within 30 days after the study is completed.
14. Be an Investigator, employee, or otherwise be directly affiliated with the study site, Watson Laboratories Inc. and affiliates, or service provider involved in the study including being an immediate family member of an Investigator or site employee (where immediate family member is defined as spouse, parent, child or sibling, whether biological or legally adopted or in foster care).
15. Non-compliance with the study requirements, rules, and procedures.

**Primary
Endpoints**

- Baseline-corrected (change from baseline) area under the serial FEV₁-time effect curve calculated from time zero to 12 hours (FEV₁ AUC₀₋₁₂) on the first day of the randomized treatment (Visit 2, Day 1) to assess equivalence of test drug (from Watson Laboratories Inc.) with RLD Symbicort 80/4.5 mcg, and to assess superiority over placebo.
- Baseline-corrected (change from baseline) FEV₁ measured in the morning prior to the dosing of inhaled medications on the last day of a 6-week treatment (Visit 4, Day ~42) to assess equivalence of test drug (from Watson Laboratories Inc.) with RLD Symbicort 80/4.5 mcg, and to assess superiority over placebo.

**Safety
Measurements**

- Forced vital capacity (FVC) results at the same time points as the FEV₁ measurements.
- Daily rescue medication use.
- Daily peak expiratory flow rate (PEFR) (morning and evening) at home.
- Symptom scores and daily symptoms (to be recorded in the electronic diary [eDiary]).

- Adverse drug reactions throughout.
- Concomitant medications at screening and updated with all new concurrent medications at all other visits.
- Daily SABA use recorded at home in the eDiary.
- Daily PEFr recorded at home in the eDiary.
- Spirometry (FEV₁, FVC, FEV₁/FVC) at screening and all other visits.
- Vital signs (blood pressure, pulse, respiratory rate, and body temperature) at all visits.
- Physical examination at screening and Visit 4 (or early termination visit).
- Clinical laboratory investigation (clinical chemistry, hematology, urinalysis) at screening. These tests will be repeated at Visit 4 (or early termination) and at any time during the study at the Investigator's discretion. Abnormal values which are deemed clinically significant will be rechecked at suitable time intervals.
- Serum pregnancy (β-hCG) test at screening and Visit 4 (or early termination); urine pregnancy test at Visit 2.
- 12-lead ECG at screening and Visit 4 (or early termination).
- Demographics and medical history at screening.
- Height, weight, and BMI at screening.
- Drug/alcohol/cotinine screen at screening.

Other Assessments

Statistical Methods

For this pivotal study, equivalence will be based on the test/reference (T/R) ratio for the 2 co-primary endpoints. The 90% confidence intervals (CI) for both T/R ratios for the primary endpoints should fall within the limits of 80.00-125.00%. Actual values without the logarithms will be used in the models.

A separate analysis of covariance (ANCOVA) model will be fit to each of the primary endpoints. The model will contain a main effect for treatment arm (one degree of freedom; DF) and center. The baseline FEV₁ will be included as a covariate. The corresponding 90% CIs for the (T/R) ratios will be calculated using Fieller's theorem. Equivalence analyses will be done on the PPS.

To ensure adequate study sensitivity, the test and reference products should both be statistically superior in terms of differences to placebo (p<0.05, 2-sided) with regard to the study primary endpoints.

Superiority will be assessed using a similar ANCOVA model as described above, for both pairs of compared treatments. Analysis of study sensitivity will be done on the mITT set.

The symptom scores and other variables will be collected descriptively.

Vital signs and ECGs will be recorded and tabulated.

Safety and tolerability data will be recorded and tabulated. The number and percentage of patients experiencing at least

1 treatment-emergent adverse event (TEAE) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class (SOC) and preferred term (PT), by treatment in total (N, incidence) and for the different levels of intensity and relationship to study drug.

SCHEDULE OF PROCEDURES

The Schedule of Procedures, as outlined in Table 1, consists of a Run-in Period and a Treatment Period.

Table 1: Schedule of Procedures

Procedure / Assessment	Screening	Run-in Period ⁽¹⁾	Treatment Period				
	Visit 1 Day -14	Day -13 to Day -1 ⁽²⁾	Visit 2 Day 1 +7 days*	Day 2-20	Visit 3 Day 21 ±7 days*	Day 22-41	Visit 4 / ET ^(3, 4) Day 42 +7 days*
Informed consent/assent ⁽⁵⁾	X						
Check inclusion / exclusion criteria (and randomization eligibility criteria at Visit 2)	X		X				
Randomization			X				
Demographics / medical history	X						
Height / weight / BMI	X						
Vital signs ⁽⁶⁾	X		X		X		X
Physical examination	X						X
12-lead resting ECG ⁽⁷⁾	X						X
Drug / alcohol / cotinine screen	X						
Clinical laboratory investigation	X						X
Serum pregnancy test	X						X
Urine pregnancy test			X		X		
Screening spirometry with reversibility testing ^(8, 9)	X						
Pre-dose and/or trough spirometry ⁽¹⁰⁾			X ⁽⁸⁾		X		X
Serial spirometry up to 12 hours post-dose ⁽¹¹⁾			X				
Dispense peak flow meters	X						
Device training (screening) and reminders ⁽¹²⁾	X		X		X		
Dispense rescue medication	X		X ⁽¹³⁾		X ⁽¹³⁾		

Procedure / Assessment	Screening	Run-in Period ⁽¹⁾	Treatment Period				
	Visit 1 Day -14	Day -13 to Day -1 ⁽²⁾	Visit 2 Day 1 +7 days*	Day 2-20	Visit 3 Day 21 ±7 days*	Day 22-41	Visit 4 / ET ^(3, 4) Day 42 +7 days*
Dispense study drug	X ⁽¹⁵⁾		X		X		
Resupply rescue medication ⁽¹⁶⁾					X		
Collect study drug			X ⁽¹⁵⁾		X		X
Inhalation of study drug at the site	X ⁽¹⁵⁾		X ⁽¹⁶⁾		X ⁽¹⁶⁾		X ⁽¹⁶⁾
PEFR measurements, inhalation of study drug by patients at home		X ⁽¹⁵⁾		X		X	
Dispense eDiary	X						
Patient completion of eDiary (daily), including: Daily symptoms Asthma symptom scores Study drug use Rescue medication use PEFR measurements		X	X	X	X	X	
Review eDiary, and check medication compliance			X		X		X
Asthma symptom score at site			X		X		X
Collect eDiary							X
AE review	X		X		X		X ⁽³⁾
Concomitant medications	X		X		X		X
Discharge from study							X

Abbreviations: AE: adverse event, BMI: body mass index, ECG: electrocardiogram, ET: Early Termination, FEV₁: forced expiratory volume in 1 second, PEFR: peak expiratory flow rate, pMDI: pressurized metered dose inhaler, QTc: corrected QT interval.

* Time window (days).

1. During the Run-in Period, patients will perform PEFR measurements and inhale placebo medication at approximately 12-hour intervals for a minimum of 14 days and maximum of 21 days.
2. There is NO Day 0.
3. The patient will be reminded to report any adverse experiences that occur within 30 days after the last visit.
4. If a patient discontinues the study prematurely, he/she will be invited to undergo an early termination visit with the same procedures as on Visit 4, except for inhalation of the study drug. More specifically, a series of at least 3 spirometric measurements will be obtained in the morning with an interval of approximately 20 minutes in between. A medical follow-up examination including physical examination, blood pressure, pulse, ECG and clinical laboratory investigation will be done.
5. Informed consent/assent may be signed up to 14 days prior to Visit 1. Written informed consent/assent must be obtained prior to any study-related procedure which includes medication washout and restrictions.
6. Blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be measured at each clinical visit after at least 10 minutes rest in supine position. On Visits 2, 3, and 4, measurements will be done in the morning prior to inhalation, and a patient would not be administered study drug if his/her blood pressure or pulse is deemed as clinically significant abnormal by the Investigator.
7. 12-lead ECG to be measured after at least 10 minutes rest in supine position.
8. Screening spirometry must demonstrate a pre-bronchodilator FEV₁ of $\geq 45\%$ and $\leq 85\%$ of the predicted value and at least 80% of the Visit 1 value. In the morning of the first day of treatment (Visit 2) the FEV₁ must also be in the range of $\geq 45\%$ and $\leq 85\%$ of the predicted value.
9. Patients must demonstrate $\geq 15\%$ reversibility of FEV₁ within 30 minutes following 360 mcg of albuterol/400 mcg salbutamol inhalation pMDI. If the patient achieves $< 15\%$, but $\geq 10\%$ reversibility at Visit 1, the site may instruct the patient to hold LABA and/or ICS and return up to 7 days later for a repeat test. Only 1 repeat of the Visit 1 spirometry (to retest reversibility) is allowed per screening.
10. Spirometric measurements in the morning prior to the dosing of inhaled medication at 60, 30, and 5 minutes pre-dose.
11. Must be performed at 60, 30 and 5 minutes pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose on the first day of the 6-week Treatment Period (Visit 2).
12. Inhalation training using placebo devices will be performed at the screening visit (Visit 1). Patients will inhale from a placebo pMDI. [REDACTED]. Patients will be instructed to use the inhaler in the morning at approximately the same time every day between 6:30 am and 11:00 am, and then approximately 12 hours later between 6:30 pm and 11:00 pm every day for the full duration of the Run-in Period and the Treatment Period. At each subsequent visit, the correct inhalation technique will be reinforced by the Investigator in the morning prior to inhalation. Patients will keep the placebo pMDI for use during the Run-in Period.
13. If a re-supply is needed.
14. If needed.

15. Open-label placebo medication will be inhaled during the Run-in Period. If a patient is deemed to be suitable to enter the Run-in Period, the first dose of placebo medication will be inhaled at the study site at Visit 1, and the correct inhalation technique will be reinforced.
16. Patients will be instructed to withhold the study drug and not perform morning PEFr measurements until they arrive at the study site. Visits must be scheduled to allow completion of the relevant assessments prior to taking study drug at the patient's regular morning time. The last dose of study drug will be inhaled at Visit 4 in the morning. Then, the inhaler will be collected.

LIST OF STUDY PERSONNEL

A list of personnel and organizations responsible for the conduct of the study will be supplied by the contract research organization (CRO) to study sites, as part of the Investigator Site File (ISF). This list will be updated by the CRO on behalf of the Sponsor and provided to study sites, as needed.

Sponsor Watson Laboratories Inc.
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054, USA

Sponsor Representative

[REDACTED]

**Pharmacovigilance/
Safety Reporting
(US and Canada)**

Teva Pharmacovigilance USA
425 Privet Road
Horsham, PA 19044

[REDACTED]

Refer to Section 6.3.4 for details of SAE reporting.

Investigators

This is a multicenter study. A list of participating Investigators, including contact details, will be maintained in the Trial Master File (TMF), including signature pages of this study protocol.

**Contract Research
Organization**

[REDACTED]

CRO Medical Monitor

[REDACTED]

CRO Project Manager

[REDACTED]

CRO Statistician

Contact details will be maintained in the TMF.

CRO Data Management

Contact details will be maintained in the TMF.

CRO Monitors

A list of responsible monitors, including contact details, will be maintained in the TMF.

Drug Packaging & Distribution (CSM)

[REDACTED]

Retention sample storage

[REDACTED]

Central Laboratory

[REDACTED]

Spirometry



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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ANCOVA	Analysis of covariance
ANDA	Abbreviated new drug application
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC	Area under curve
AUC ₀₋₁₂	Area under the serial FEV ₁ time effect curve calculated from time zero to 12 hours (FEV ₁ AUEC ₀₋₁₂)
β-hCG	Beta-human chorionic gonadotropin
BDRM	Blinded Data Review Meeting
BDS 80/FFD 4.5	Generic budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg (as developed by Watson Laboratories Inc.)
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRO	Contract research organization
CV	Coefficient variance
DF	Degrees of freedom
eCRF	Electronic case report form
ECG	Electrocardiogram
eDiary	Electronic diary
ENS	Enrolled Set
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV ₁	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
hCG	Human chorionic gonadotropin
IB	Investigator's brochure

ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LABA	Long-acting β 2-adrenergic agonist
LOCF	Last observation carried forward
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat (set)
NAEPP	National Asthma Education and Prevention Program Expert Panel Report
NHANES	National Health and Nutrition Examination Survey
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PID	Patient identification
PIF	Peak inspiratory flow rate
pMDI	Pressurized metered dose inhaler
PT	Preferred term
PPS	Per-Protocol Set
QTc	Corrected QT interval
RiN	Run-in Set
RLD	Reference listed drug
SABA	Short-acting β agonist
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
SOC	System organ class
SPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event

T/R	Test/reference ratio
US	United States (of America)
WHO-DRL	World Health Organization – Drug Reference List
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background

Asthma is a serious public health problem throughout the world, affecting about 300 million individuals of all ages. Asthma is a chronic inflammatory disorder of the airways, characterized by recurrent acute attacks of breathlessness and wheezing, in which many cells and cellular elements play a role [1]. When uncontrolled, asthma can place severe limitations on daily life, and is sometimes fatal. Although there is no cure, avoidance of asthma triggers and the use of appropriate long- and short-term medication offer patients options for control of their disease [2].

Inhaled corticosteroids (ICSs) are recommended as first-line treatment for patients with persistent asthma, and the addition of an inhaled long-acting β 2-adrenergic agonist (LABA) can be considered to improve lung function and symptoms in patients whose asthma is not well controlled on ICS alone. Combination therapy has become the standard of care for the treatment of mild to moderate persistent asthma [3], [4], [5]. Clinical long-term experience over the last decade has shown that regular inhalational treatment with fixed combinational ICS/LABA products results in substantial increases in relevant lung function parameters (forced expiratory volume in 1 second [FEV₁] and peak expiratory flow [PEF]) and clinical symptom control [3], [4]. Further it has been shown that ICS/LABA combinations do not cause any tolerance development of asthma control, rendering fixed ICS/LABA combinations currently the most effective and beneficial long-term treatments of asthma available.

Symbicort[®] is a combination product containing a corticosteroid (budesonide) and a LABA (formoterol fumarate dehydrate), indicated for the treatment of asthma in patients 12 years of age and older and for maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema [6]. It is not indicated for the relief of acute bronchospasm. Symbicort[®] is marketed in the US as Symbicort[®] and in Europe as Symbicort Turbohaler[®].

Watson Laboratories Inc. is developing a generic form of budesonide/formoterol fumarate dihydrate inhalation aerosol delivered via a pressurized metered dose inhaler (pMDI) device. The device is a disposable canister containing a combination of micronized budesonide (80 mcg per actuation) and micronized formoterol fumarate dihydrate (4.5 mcg per actuation) as an oral inhalation aerosol formulation. It is a pMDI developed as generic to the United States (US) reference listed drug (RLD) Symbicort[®] for the treatment of asthma and COPD.

Further details can be found in the Investigator's Brochure (IB), which contains comprehensive information on the investigational product.

The current study is designed to establish the therapeutic equivalence of Watson Laboratories Inc.'s generic formulation to commercially available Symbicort[®]. It is a randomized, multiple-dose, placebo-controlled, parallel group design consisting of a 2-week open placebo Run-in Period followed by a 6-week randomized Treatment Period with either test product, RLD, or placebo. Male and female adolescents and adults who have asthma will self-administer study drug twice daily.

1.2 Rationale

This study is part of a program considered necessary by the US Food and Drug Administration (FDA) for getting approval for a generic inhalation product. Generally, in the absence of a product specific guidance the FDA suggests that to support the “weight of evidence” for approval of an abbreviated new drug application (ANDA) a pivotal therapeutic equivalence study with clinical endpoint should be done comparing test product and RLD with regard to clinical efficacy.

This study is designed to evaluate bioequivalence between the test product and RLD in accordance with the recommendations outlined in the US FDA Draft Guidance on Budesonide; Formoterol fumarate dihydrate (June 2015) [7].

1.3 Risk-Benefit Assessment

The risks of participation in this study are mainly related to the possibility of loss of asthma control and resulting morbidity in patients randomized to the placebo group, or not responding to therapy, and the adverse effects of budesonide/formoterol fumarate therapy.

The adverse effect profile of generic budesonide/formoterol fumarate therapy is expected to be the same as for the RLD, Symbicort[®]. The adverse effect profile of Symbicort[®] is well established [6]. Symbicort[®] has a Black Box Warning in the US which states:

ASTHMA-RELATED DEATH:

- LABA, such as formoterol one of the active ingredients in Symbicort[®], increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of ICS or other long-term asthma control drugs mitigates the risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.
- When treating patients with asthma, prescribe Symbicort[®] only for patients not adequately controlled on a long-term asthma control medication, such as inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue Symbicort[®]) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use Symbicort[®] for patients whose asthma is adequately controlled on low or medium dose ICS.

The prescribing information [6] also includes the following ICS-related warning:

- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue Symbicort[®] slowly.

The available information suggests that the present study has a favorable risk-benefit ratio. The study design includes strict withdrawal criteria for worsening asthma during

both the 2-week placebo Run-in Period and 6-week randomized Treatment Period, and the availability of rescue medication ensures that no patient is placed at undue risk. The risk of ICS-related effects is minimized because the recommended daily dose will not be exceeded.

2 STUDY OBJECTIVES

2.1 Primary Objective

The objective of this pivotal trial is to confirm the therapeutic equivalence of a new generic fixed-dose combination product containing budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg (BDS 80/FFD 4.5) (per actuation) inhalation aerosol pMDI manufactured by [REDACTED] for Watson Laboratories Inc. and RLD Symbicort[®] (budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg inhalation aerosol) manufactured by AstraZeneca, in adolescent patients and adult patients with chronic but stable asthma as defined in National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPP 3) guidelines [8].

To ensure adequate study sensitivity the test and reference products should both be statistically superior to placebo ($p < 0.05$) with regard to the bioequivalence study primary endpoints.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a randomized, blinded, parallel group, placebo-controlled, multiple dose, multicenter, multinational study to compare the therapeutic equivalence of BDS 80/FFD 4.5 (per actuation) inhalation aerosol pMDI manufactured by ██████████ for Watson Laboratories Inc. and RLD Symbicort[®] manufactured by AstraZeneca, in adolescent patients and adult patients with chronic but stable asthma as defined in NAEPP 3 guidelines.

All patients in this study must have a documented diagnosis of moderate to severe asthma. Male patients and non-pregnant, nonlactating female patients 12 years to 75 years of age who meet the entry criteria may be enrolled.

The study consists of a 2-week open placebo Run-in Period followed by a 6-week randomized Treatment Period (test, reference, or placebo).

Written informed consent/assent must be obtained prior to any study-related procedure which includes medication washout and restrictions. Informed consent/assent may be signed up to 14 days prior to Visit 1.

Screening Visit

Patient demographic information, medical and asthma history, lung function, and clinical laboratory assessments will be collected after patients provide informed consent/assent (the latter for adolescent patients) and before taking study drug. Laboratory values at screening must be normal (or abnormal and not clinically significant) as evaluated by the Investigator.

At Visit 1, patients will perform spirometry to demonstrate a pre-bronchodilator FEV₁ of $\geq 45\%$ and $\leq 85\%$ of the predicted normal value using the equations derived from the National Health and Nutrition Examination Survey (NHANES) III dataset for adults [9]. All lung function tests will be conducted in accordance with current American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations [10].

Patients must demonstrate $\geq 15\%$ reversibility of FEV₁ within 30 minutes following 360 mcg (4 puffs) of albuterol (free base) or 400 mcg (4 puffs) of salbutamol inhalation (pMDI) at screening (Visit 1). Up to 2 spirometry sessions within the time window after bronchodilator administration (30 minutes \pm 10 minutes) are permitted at Visit 1. If the patient achieves $< 15\%$, but $\geq 10\%$ reversibility at Visit 1, the site may instruct the patient to hold LABA and/or ICS and return up to 7 days later for a repeat test. Only 1 repeat of the Visit 1 spirometry (to retest for reversibility) is allowed per screening.

Patients will receive instruction on how to measure PEF rate (PEFR) and answer electronic diary (eDiary) questions asking the patient about his/her asthma symptoms. Patients will also be instructed to measure PEFR and answer the questions before self-administering the provided study drug. Patients will also be given an albuterol/salbutamol pMDI as rescue medication and instructed to use 2 inhalations of albuterol/salbutamol as needed to relieve asthma symptoms.

Open Label Placebo Run-in Period

Eligible patients will enter an open label, placebo Run-in Period of at least 2 weeks in duration (but not longer than 21 days) to wash out any pre-study corticosteroids or long-acting bronchodilators and to establish FEV₁ baseline values.

Patients will perform PEFr measurements and inhale placebo medication at approximately 12 hour intervals for a minimum of 14 days and maximum of 21 days.

Patients must have placebo inhaler compliance of at least 75% of study drug doses in the Run-in Period to proceed into the randomized Treatment Period. Compliance will be based on patient eDiary.

Randomized Treatment Period

Those continuing to meet entry criteria will enter a 6-week Treatment Period (that begins on the following day, Day 1) and be randomly assigned in a 4:4:1 ratio to 1 of 3 treatment arms:

- Test product: BDS 80/FFD 4.5 inhalation aerosol (manufactured by ██████ for Watson Laboratories Inc.) (test)
- Reference product (RLD): Symbicort[®] (manufactured by AstraZeneca) (reference)
- Placebo: To match generic BDS 80/FFD 4.5 inhalation aerosol (manufactured by ██████ for Watson Laboratories Inc.) (placebo)

On the first day of treatment at Visit 2, FEV₁ will be determined at 60, 30, and 5 minutes pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose.

Patients will record PEFr data and the other requested information on their eDiary and take test, reference, or placebo at approximately 12 hour intervals for a minimum of 42 days and maximum of 49 days.

Patients will be instructed to return to the clinic for Visit 3 at the end of the third treatment week (treatment day 21 ± 7 days) and for Visit 4, at the end of the sixth treatment week (treatment day 42 + a time window of 7 days). Patients will be instructed to withhold the study drug and not perform morning PEFr measurements until they arrive at the clinic on the morning of Visit 3 (Day 21 ± 7 days) and Visit 4 (Day 42 + 7 days). On both visits, FEV₁ will be determined at 60, 30, and 5 minutes pre-dose, the average of which constitutes the pre-dose (0) value. A minimum of 2 pre-dose values are required to estimate the mean/average.

At the beginning of each visit, the Investigator will thoroughly review the patient's eDiary entries and discuss the results with the patient. The patients will be asked about their medication washouts and whether they have experienced any unusual symptoms or medical problems since the last visit. Patients will be reminded that they must inhale the study drug as instructed.

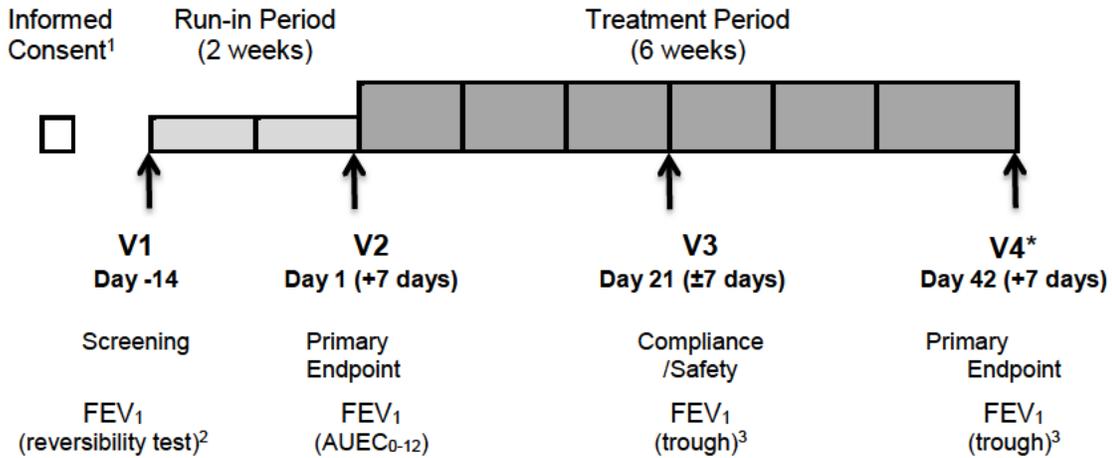
Overall, the planned duration of patient participation is 8 weeks comprising 2 weeks for the placebo Run-in Period and 6 weeks for the randomized Treatment Period.

No formal interim analysis with statistical stopping rules will be undertaken, although sample size recalculation may be performed per the interim analysis plan (Section 8.10).

After the end of the study, the patients will revert to their previous care plan.

A detailed Schedule of Procedures is provided in Table 1. A schematic of the study design is provided in Figure 1.

Figure 1: Overall Study Design



* The patient will be reminded to report any adverse experiences that occur within 30 days after the last visit.

¹ Written informed consent/assent must be obtained prior to any study-related procedure which includes medication washout and restrictions. Informed consent/assent may be signed up to 14 days prior to Visit 1.

² A repeat of the Visit 1 spirometry (to retest for reversibility) may be required up to 7 days after Visit 1; this will require an extension to the screening (Visit 1).

³ Change from baseline.

AUC₀₋₁₂=area under the curve from 0 to 12 hours, FEV₁: Forced expiratory volume in 1 second, V: visit.

3.2 Criteria for Evaluation of the Study

3.2.1 Primary Endpoints

This pivotal study will examine the following co-primary endpoints:

- Baseline-corrected (change from baseline) area under the serial FEV₁-time effect curve calculated from time zero to 12 hours (FEV₁ AUC₀₋₁₂) on the first day of the randomized treatment (Visit 2, Day 1) to assess equivalence of test drug (from Watson Laboratories Inc.) with RLD Symbicort 80/4.5 mcg.
- Baseline-corrected (change from baseline) FEV₁ measured in the morning prior to the dosing of inhaled medications on the last day of a 6-week treatment (Visit 4, Day ~42) to assess equivalence of test drug (from Watson Laboratories Inc.) with RLD Symbicort 80/4.5 mcg.

To ensure adequate study sensitivity, the test and reference products should both be statistically superior to placebo (p<0.05) with regard to the bioequivalence study primary endpoints.

An FEV₁ baseline is defined as the average of all pre-dose FEV₁ values (e.g., at least 2 non-missing time points are required for a valid baseline) measured in the morning of the first day of the 6-week randomized Treatment Period. Measurements will correspond to the same time of day as used on the last day of the 6-week treatment. On the first day of the 6-week Treatment Period, FEV₁ will be determined at 60, 30, and 5 minutes

pre-dose (the average of which constitutes the pre-dose (0) value), and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hour post-dose. At the end of the 6-week Treatment Period, FEV₁ will be determined at 60, 30, and 5 minutes pre-dose on ~Day 42 morning dose (constituting the trough values).

3.2.2 Safety Measurements

- Forced vital capacity (FVC) results at the same time points as the FEV₁ measurements.
- Daily rescue medication use.
- Daily PEFr (morning and evening) at home.
- Symptom scores and daily symptoms (to be recorded in the eDiary).
- Adverse reactions throughout.
- Concomitant medications throughout.
- Daily short-acting β agonist (SABA) use recorded at home in the eDiary.
- Daily PEFr recorded at home in the eDiary.
- Spirometry (FEV₁, FVC, FEV₁/FVC) at screening and all other visits.
- Vital signs at all visits.
- Physical examination at screening and Visit 4 (or early termination visit).
- Clinical laboratory investigation at screening and Visit 4 (or early termination).
- Serum pregnancy (β -hCG) test at screening and Visit 4 (or early termination); urine pregnancy test at Visit 2.
- 12-lead electrocardiogram (ECG) at screening and Visit 4 (or early termination).

3.2.3 Other Assessments

- Demographics and medical history at screening.
- Height, weight, and BMI at screening.
- Drug/alcohol/cotinine screen at screening.

3.3 Justification of the Study Design

The design of this study follows the recommendation of the FDA draft guidance document on Budesonide; Formoterol fumarate dihydrate (June 2015) [7].

This FDA guidance requires that patients discontinue previous asthma-controller therapy during the 2-week Run-in Period. After the Run-in Period, patients are randomly assigned to either the test, reference, or placebo treatment. Patients continue to use the study-supplied rescue medication (i.e., albuterol/salbutamol inhaler) throughout the 6-week Treatment Period. Patients are also blinded to the identity of the study drug during the Treatment Period.

4 STUDY POPULATION

The study population will consist of male and non-pregnant female patients (≥ 12 and ≤ 75 years of age) with moderate to severe asthma as defined by the NAEPP 3 guidelines [8]. Patients must be able to provide written consent/assent and meet all the inclusion criteria and none of the exclusion criteria.

4.1 Inclusion Criteria

Patients will be entered into this study only if they meet all of the following criteria:

1. Adolescent and adult male or female patients (≥ 12 and ≤ 75 years of age)
2. Female patients must not be lactating or pregnant at screening, as documented by a negative serum pregnancy test with a minimum sensitivity of 25 IU/L or equivalent units of beta-human chorionic gonadotropin (β -hCG) at screening.
3. Women of childbearing potential (WOCBP) and female partners (WOCBP) of male patients participating in the study, must commit to consistent and correct use of an acceptable method of birth control (at the Investigator's discretion) throughout the study and for 30 days after study drug discontinuation.
4. Male patients and male partners of female patients (WOCBP) must commit to consistent and correct use of an acceptable method of birth control (at the Investigator's discretion) throughout the study and for 30 days after the study drug discontinuation.
5. Diagnosed with asthma as defined by the NAEPP 3 [8] at least 6 months prior to screening. If the patient is new to the study site, the Investigator must confirm the patient's asthma diagnosis. Acceptable means include either medical records or pharmacy records.
6. Moderate to severe asthma with a pre-bronchodilator FEV₁ of $\geq 45\%$ and $\leq 85\%$ of the predicted normal value during measured at least 6 hours after SABA and at least 24 hours after the last dose of LABA at the screening visit (Visit 1) and on the first day of treatment (prior to randomization at Visit 2).
7. Currently non-smoking, negative for urine cotinine at screening, having not used tobacco products (i.e., cigarettes, cigars, pipe tobacco, electronic cigarettes) within the past year, and had ≤ 10 pack-years of historical use.
8. Body mass index (BMI) between 18 and 40, inclusive for patients ≥ 18 years old. For adolescent patients 12 to 17 years old, BMI between 15 and 40 inclusive (in accordance with the BMI range typical for the age) (refer to Appendix 11.2 for guide to lower limits of BMI in adolescents).
9. $\geq 15\%$ and ≥ 0.20 L reversibility of FEV₁ within 30 minutes following 360 mcg (4 puffs) of albuterol (400 mcg salbutamol) inhalation (pMDI). If the patient achieves $< 15\%$, but $\geq 10\%$ reversibility at Visit 1, the site may instruct the patient to hold LABA and/or ICS and return in up to 7 days for a repeat test. Only 1 repeat of the Visit 1 spirometry (to retest reversibility) is allowed per screening.

10. Able to perform valid and reproducible spirometry per ATS/ERS standards [10] at screening.
11. Able to inhale study drug properly.
12. Willing to discontinue asthma medications (ICS and LABAs) during the Run-in Period and for the remainder of the study.
13. Able to replace current regularly scheduled SABAs with albuterol/salbutamol inhaler for use only on as-needed basis for the duration of the study (patients should be able to withhold all inhaled SABAs for at least 6 hours prior to lung function assessments on study visits).
14. Able to continue the following medications without a significant adjustment of dosage, formulation, dosing interval for the duration of the study, and judged able by the Investigator to withhold them for the specified minimum time intervals prior to each clinic visit, if applicable:
 - Short-acting forms of theophylline: 12 hours.
 - Twice-a-day controlled-release forms of theophylline: 24 hours.
 - Once-a-day controlled-release forms of theophylline: 36 hours.
15. Able to discontinue the following medications for the specified minimum time intervals prior to the Run-in Period and for the remainder of the study, if applicable:
 - Oral corticosteroids for 30 days.
 - Parenteral corticosteroids for 30 days.
 - Oral (not inhaled) SABAs for 24 hours.
16. Clinical laboratory tests (clinical chemistry, hematology, and urinalysis) and 12-lead ECG conducted at the screening visit within normal limits or abnormal but not clinically significant to the Investigator. The QTc should be calculated using Bazett's formula.
17. Willing to give written informed consent/assent, and willing and able to follow the study rules and procedures.
18. Stable on chronic asthma treatment regimen for at least 4 weeks prior to enrollment
19. Ability to perform forced expiratory assessments according to ATS standards.

4.2 Randomization Eligibility Criteria

1. Baseline pre bronchodilator FEV₁ should be $\geq 45\%$ and $\leq 85\%$ of predicted normal value and not vary by more than $\pm 20\%$ from the screening visit FEV₁ value.
2. Compliance during the Run-in Period of at least 75% (based on eDiary entries) is required for a patient to qualify for randomization. Compliance with the run-in placebo treatment must be between 75% and 125%.
3. Documented total asthma symptom score of ≥ 1 for at least 2 days during the Run-in Period.

4.3 Exclusion Criteria

Patients will be entered into this study only if they meet none of the following criteria:

1. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnea, respiratory arrest or hypoxic seizures, asthma-related syncopal episode(s), or hospitalizations within the past year or during the Run-in Period.
2. Exercise-induced asthma as the only asthma-related diagnosis.
3. Evidence or history of clinically significant disease or abnormality including congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, or cardiac dysrhythmia. In addition, historical or current evidence of significant hematologic, hepatic, neurologic, psychiatric, renal, or other diseases that in the opinion of the Investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbated during the study. Patients with well controlled hypertension, diabetes, or hypercholesterolemia are not excluded as long as their medication does not interfere with the study.
4. Any other clinically relevant pulmonary disease except for asthma, including COPD, interstitial lung disease, cystic fibrosis, bronchiectasis, chronic bronchitis, emphysema, active pulmonary tuberculosis, pulmonary carcinoma, pulmonary fibrosis, or pulmonary hypertension. In addition, obstructive sleep apnea warranting a prescription for continuous or biphasic positive airway pressure (CPAP or BiPAP).
5. Patients who required systemic corticosteroids (for any reason) within the past 4 weeks.
6. Patients with hypersensitivity to any sympathomimetic drug (e.g., formoterol, albuterol/salbutamol, or salmeterol) or any inhaled, intranasal, or systemic corticosteroid therapy.
7. Patients taking medication(s) (either daily or as needed) with the potential to affect the course of asthma or to interact with sympathomimetic amines, e.g.,:
 - Oral β -blockers.
 - Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir).
 - Monoclonal antibodies/Biologic agents which may affect the course of asthma (such as mepolizumab, reslizumab, lebrikizumab, and others).

Refer to Section 5.9 for relevant washout periods

8. Viral or bacterial, upper or lower respiratory tract infection or sinus or middle ear infection within 2 weeks prior to the screening visit or during the Run-in Period.
9. Factors (e.g., infirmity, disability or geographic location) that the Investigator feels would likely limit the patient's compliance with the study protocol or scheduled clinic visits.
10. Anti-IgE (such as omalizumab) within the 6 months prior to screening.
11. History of alcohol or drug abuse within the last 6 months.

12. A positive urine drug screen at Visit 1. Exceptions are made for a positive urine drug screen at Visit 1 for opiates or stimulants if there is a documented prescription with supporting medical history and diagnosis, and the Principal Investigator assesses there are no safety concerns with patient participation. Screened patients with a urine drug screen positive for Marijuana/Tetrahydrocannabinol (THC) are not eligible for study participation, without exceptions. Repeat drug screening is not allowed.
13. Have received any investigational treatment within 30 days (or within 5 terminal half-lives of the investigational drug whichever is longer) of the screening visit or plans to receive investigational treatment within 30 days after the study is completed.
14. Be an Investigator, employee, or otherwise be directly affiliated with the study site, Watson Laboratories Inc. and affiliates, or service provider involved in the study including being an immediate family member of an Investigator or site employee (where immediate family member is defined as spouse, parent, child or sibling, whether biological or legally adopted or in foster care).
15. Non-compliance with the study requirements, rules, and procedures.

4.4 Patient Withdrawal and Replacement

Patients may withdraw from the study at any time without penalty and for any reason without prejudice to his or her future medical care. Patients may be required to withdraw from study at discretion of the Investigator after discussion with the Sponsor and/or Investigator.

4.4.1 Withdrawal Criteria for Asthma Exacerbation

Asthma-related Withdrawal Criteria at Visit 2:

- FEV₁ at Visit 2 is less than 80% of the Visit 1 value.
- Use of rescue inhaler at any point during the post-dose 12-hour spirometry during Visit 2.

Investigators may withdraw patients for overuse of rescue medication that, in their opinion, demonstrates inadequate asthma control that could put the patient at risk.

Asthma Exacerbation:

Patients who experience a severe asthma exacerbation should be withdrawn from the study, and receive treatment according to individual needs. A patient is considered to be experiencing a severe exacerbation if one or more of the below conditions is experienced:

- Need for oral and/or parenteral corticosteroids.
- Need for medication that's not allowed by the protocol.
- Asthma-related unscheduled clinic visit (should only be a cause for withdrawal if found to be clinically significant by the Investigator).
- Asthma-related visits to the emergency department.
- Need for hospital admission due to asthma.

Patients who require resumption of their prior ICS controller therapy, introduction of oral or injectable corticosteroids and/or a LABA after the onset of an exacerbation should be withdrawn.

The primary reason for withdrawal for patients who discontinue from the study because of asthma symptoms should be entered into the electronic case report form (eCRF) as “lack of efficacy”, not an adverse event (AE) or serious AE (SAE). However, severe asthma exacerbations occurring during the study should be reported as an AE in the eCRF (Section 6.3).

4.4.2 Additional Withdrawal Criteria

Patients **must** be withdrawn at any time during the study under the following circumstances:

- The patient becomes pregnant (see Section 6.3.8).
- The patient has an AE that would, in the Investigator’s judgment, make continued participation an unacceptable risk.
- The patient is judged by the Investigator to be significantly noncompliant with the requirements of the protocol.
- A patient may also be withdrawn from the study by the Sponsor, Regulatory Authorities, or Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Patients will also be withdrawn if the entire study is terminated prematurely as described in Section 9.10.

4.4.3 Withdrawal Procedures

If a patient withdraws consent/assent to participate after taking at least 1 dose of randomized study drug but agrees to undergo final assessments, this will be documented on the eCRF and the Investigator’s copy of the consent/assent document, which will be countersigned and dated by the patient or his/her parent or legal guardian (if the patient is not of legal age).

In all cases, the primary reason for withdrawal must be recorded on the eCRF. If a patient is prematurely withdrawn from the study drug for any reason, the Investigator must make every effort to perform the evaluations described for the End-of-Study visit.

Patients who do not complete the Run-in Period (i.e., patients who withdraw before Visit 2 randomization) will be replaced. Patients who withdraw (or are withdrawn) from the study after receiving the first dose of randomized study drug will not be replaced. Assessments to be performed in case or early withdrawal are specified in Section 7.1.5.

4.5 Planned Sample Size and Number of Study Centers

Approximately 1130 patients at up to ■ sites in the US will be randomized for this study. Sites in Europe may be considered in case recruitment is lower than expected in US sites. See Section 8.11 for a discussion of sample size.

4.6 Patient Identification and Randomization

4.6.1 Patient Identification

Upon enrollment into the study (i.e., Visit 1, Screening), each patient will be sequentially assigned a 6-digit patient identification (PID) number that uniquely identifies the patient,

with the first three digits identifying the site and the last three digits identifying the patient number at the site. The PID number for each patient will be assigned via Interactive Web Response System (IWRS).

Once assigned, the PID number cannot be reused or reassigned even if a patient does not enter the randomized Treatment Period or withdraws from the study at any time. Patients who remain in the study will retain their PID numbers throughout the study.

4.6.2 Randomization Scheme

Patients will be randomly assigned to treatment on a [REDACTED] of generic BDS 80/FFD 4.5 inhalation aerosol manufactured by [REDACTED] for Watson Laboratories Inc. (test): Symbicort® (RLD): placebo (P) [T:R:P] respectively.

4.6.3 Allocation/Randomization of Patients to Treatment

Randomization of patient to treatment will occur at Visit 2 (Day 1) after all screening procedures have been performed and eligibility for the study confirmed. Each randomized patient will receive a unique randomization number assigned via IWRS. Randomized patients who terminate their study participation for any reason, regardless of whether study drug was taken or not, will retain their randomization number.

For the randomization of patients, the Investigator will use an IWRS. Appropriate documentation will be filed in the Trial Master File (TMF). IWRS will assign patients to a treatment group based on the pre-defined randomization list.

5 STUDY DRUG

All study drugs required for this study (test product, reference product, placebo, rescue medication) will be supplied by the Sponsor.

Run-in Period:

Placebo: Generic inhaler containing placebo aerosol for inhalation (open label).
Route: Oral inhalation.
Posology: Two inhalations twice daily, with a dosing interval of approximately 12 hours.
Duration: 14 days (up to 21 days).

Treatment Period:

Randomized Study Drug:

Test: Generic budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg (BDS 80/FFD 4.5) inhalation aerosol pMDI, manufactured by [REDACTED] for Watson Laboratories Inc..

Reference: Symbicort® (budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg inhalation aerosol, manufactured by AstraZeneca) [REDACTED].

Placebo: Generic pMDI inhaler containing placebo to match generic test product, aerosol for inhalation [REDACTED].

Dose Regimen (All Study Drugs):

Route: Oral inhalation.
Posology: Two inhalations twice daily (such that the cumulative single dose is budesonide 160 mcg/formoterol fumarate dihydrate 9 mcg twice daily) or placebo, with a dosing interval of approximately 12 hours. Last dose on the morning of Visit 4.
Duration: 42 days (35 days to 56 days).

5.1 Identity

5.1.1 Test Product

The generic test product is a metered dose inhaler (pMDI) with a canister containing a combination of budesonide and formoterol fumarate dihydrate as an inhalation aerosol. The device contains micronized budesonide and micronized formoterol fumarate as the dihydrate salt. The generic formulation is identical in composition to the reference product.

The canister contains a total of 120 pre-metered doses of budesonide/formoterol fumarate dihydrate. An "Information For Use" document for the pMDI device will be provided to all patients.

5.1.2 Reference Product

The RLD, Symbicort[®] 80/4.5, is available commercially from AstraZeneca as an inhalation aerosol of budesonide (80 mcg) and formoterol fumarate dihydrate (4.5 mcg).

Symbicort[®] is a disposable metered dose inhaler (pMDI) device with a canister containing a combination of micronized budesonide and micronized formoterol fumarate dihydrate as an inhalation aerosol. The lowest dose strength of Symbicort[®] contains budesonide and formoterol fumarate as the dihydrate salt.

After priming the low dose strength (budesonide 80 mcg and formoterol fumarate dehydrate 4.5 mcg; BDS 80/FFD 4.5 mcg), each actuation meters 91/5.1 mcg from the valve and delivers BDS 80/FFD 4.5 mcg from the actuator. The amount of drug delivered to the lungs may depend on patient factors such as coordination between actuation of the device and inspiration through the device.

The formulation contains the following excipients, which are well established pharmacopoeial excipients for inhalation products:

- Povidone (viscosity K-value K25) United States Pharmacopeia convention (USP) as suspending agent
- PEG 1000 National Formulary (NF) as lubricant
- Hydrofluoroalkane (HFA227) as propellant

The canister contains a total of 120 pre-metered doses of budesonide/formoterol fumarate dihydrate. An “Information For Use” document for the pMDI device will be provided to all patients.

5.1.3 Placebo

The placebo matches the generic test product and is composed of the inactive excipients listed in Section 5.1.2. Placebo will be manufactured by ██████████ for Watson Laboratories Inc.

The placebo inhalation aerosol is administered using a pMDI, which is similar in design and operation to the test product and the marketed product Symbicort[®]. An “Information For Use” document for the pMDI device will be provided to all patients.

5.1.4 Rescue Medication

Rescue medication is a commercially available albuterol/salbutamol inhaler 100 mcg per puff (or equivalent) that will be supplied to all study patients.

One canister will be dispensed at the screening visit (Visit 1). That canister will also be used for the reversibility test. Reserve canister(s) or re-supply will be provided as necessary. Refer also to Section 5.9.1.

5.2 Administration

All study drugs will be administered via oral inhalation. Two inhalations will be administered twice daily with a dosing interval of approximately 12 hours. Study drug doses may be taken without regard to meals. For test product and reference product, the cumulative single dose will be budesonide 160 mcg/ formoterol fumarate dihydrate

9 mcg, and cumulative daily dose will be budesonide 320 mcg/ formoterol fumarate dihydrate 18 mcg. Any dosing not recorded in the eDiary will be considered “missed”. All patients will undergo device training with the aid of a dummy/placebo device and [REDACTED] at screening, with reminders on how to use the device at subsequent visits (see Section 5.3). Patients will be instructed to use the inhaler in the morning at approximately the same time every day between 6:30 am and 11:00 am, and then approximately 12 hours later between 6:30 pm and 11:00 pm every day for the full duration of the Run-in Period and the Treatment Period. Morning doses should be withheld on scheduled study day visits and self-administered as soon as possible after the study visit assessments/procedures have been completed, as indicated in Table 1. Instructions on how to use the pMDI devices (“Information For Use” document) will be provided for all patients at the start of the placebo Run-in Period and will be provided for all randomized patients at the start of the Treatment Period. Study drug compliance is discussed in Section 8.6. All dosing must be recorded in the eDiary.

5.2.1 Run-in Period

During the Run-in Period, placebo inhalers and rescue medication will be distributed to each enrolled patient. Patients will be trained in the proper usage of the devices (see Section 5.3) and observed during administration of the first dose of placebo inhaler. The first dose of study drug in this period will be self-administered by the patient at the site after all assessments have been conducted.

Patients will record all dosing in an eDiary. Eligibility at Visit 2 will be based on compliance per patient eDiary during the Run-in Period (Section 5.8.1) and spirometry at Visit 2 (Section 6.1.1).

5.2.2 Treatment Period

At Visit 2, eligible patients will be randomly assigned to study drug (i.e., test, RLD, or placebo) (Section 5.1).

[REDACTED]

Placebo inhalers from the Run-in Period will be collected. Before taking the first dose of randomized study drug, all patients will undergo pre-dose assessments (as detailed in Table 1 and including FEV₁ measurement) and then take their first dose of randomized study drug at the site where they will be required to stay for approximately 12 hours in order to complete the serial spirometry tests (Section 6.1.1). After the serial spirometry tests are completed, patients will take their evening dose of randomized study drug and be released from the site. If needed, patients will be retrained in the proper usage of the inhalation devices.

Patients will be instructed to withhold the study drug and not perform morning PEFr measurements until they arrive at the clinic on the morning of Visit 3 (Day 21) and Visit 4 (Day 42). The last dose will be taken on the morning of Visit 4.

Patients will also be asked to bring their study drug devices with them to every on-site visit. At the patient’s final on-site visit (Visit 4), all study drug devices will be collected.

5.3 Device Training

Inhaler device training using placebo devices will be performed at the screening visit (Visit 1), with reinforcement of proper technique at subsequent visits. [REDACTED]

[REDACTED]. At each subsequent visit, the correct inhalation technique will be reinforced by the Investigator in the morning prior to dose administration. Patients will keep the placebo pMDI inhalers for use during the Run-in Period.

5.4 Packaging, Labeling, and Storage

Study drug (test, reference, and placebo) and rescue medication will be packaged, labeled, and distributed by [REDACTED]. (see List of Study Personnel) according to US and local legal and regulatory requirements.

Label text will be translated into the local language, if necessary. The label will include the name of the Sponsor, Protocol code, For Clinical Trial use only, and/or any other US-specific or market-specific requirements. A patient's leaflet will be inserted if required per local regulations.

Shipment to the sites will be in ambient controlled conditions (20 to 25°C). All study drug supplies must be stored in accordance with the manufacturer's instructions. The test, RLD, and placebo products should be stored at room temperature (20 to 25°C). Until dispensed to the patients, the study drug will be stored in a secure area, accessible to authorized personnel only.

Full details regarding receipt, storage, distribution, and return/destruction of the study drug will be provided in a pharmacy manual.

Refer to Section 5.6 for information on packaging, labeling, and dispensing rules related to maintenance of the study drug blind.

5.5 Retention of Samples

Samples of the study drug will be randomly selected, in accordance with 21 CFR 320.38, 320.63 and the Guidance for Industry "Handling and Retention of bioavailability (BA) and bioequivalence Testing Samples", regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. As stated in Section VII of the Guidance for Industry "Handling and Retention of BA and bioequivalence Testing Samples", there is an exception for inhalant products whereby, for ANDAs, in lieu of the "five times quantity" requirement, at least 50 units of each of 3 batches should be retained for each of the test articles and reference standards used for in vivo or in vitro bioequivalence studies.

The appropriate number of samples to be retained from each shipment (test, reference and placebo) will be selected through the IWRS. [REDACTED]

The retained samples from each shipment of study drug will be packaged and shipped to an independent third party storage facility as soon as possible to ensure samples are not confused with study drug for patient use and to ease the storage burden at each site. The

retained samples must be stored under appropriate conditions at the site (refer to Section 5.4) until they are shipped to the third party storage facility.

Retained samples will be kept for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the study in which the retained sample was obtained.

In addition, the Investigators should follow the procedures of 21 CFR 58 and International Conference on Harmonization (ICH) E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP).

5.6 Blinding and Breaking the Blind

Patient identification and randomization via IWRS are described in Section 4.6.

5.6.1 Blinding

Placebo for use during the Run-in Period will be open-label.

During the Treatment Period, the following blinding procedures will apply:

- [REDACTED]
- [REDACTED]
- Access to the randomization code will be strictly controlled.
- All patients will follow the same dosing scheme, i.e., 2 actuations from the applicable inhaler twice daily with a dosing interval of approximately 12 hours.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

Further details of blinding are provided in the study manual.

The biostatistician, Watson Laboratories Inc., and contract research organization (CRO) key staff will remain blinded for test, placebo and RLD product until disposition coding is completed. The Investigator must remain blinded [REDACTED] during the performance of clinical assessments. [REDACTED]

[REDACTED] Patients will be instructed not to describe their study drug, or the container in which it was dispensed, to anyone, and will be discouraged from attempting to identify their study drug, through internet searches of images of similar products.

[REDACTED]

They should also be instructed to return the inhaler in the box at each return visit and not disclose any description of the device to [REDACTED] site staff.

5.6.2 Breaking the Blind

The study blind should not be broken except in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or regulatory requirement (e.g., for a suspected unexpected serious adverse reaction [SUSAR] or US Investigational New Drug expedited report or death).

In cases where immediate need for unblinding exists for the reasons of patient safety, the Investigator can unblind the patient at his/her discretion. When possible, the Investigator should notify Sponsor/Medical Monitor before contacting IWRS. All calls resulting in an unblinding event will be recorded and reported by the IWRS to the Medical Monitor and the Sponsor. If the blind is broken, the date, time, and reason must be recorded in the patient's eCRF and any associated AE report.

Serious, unexpected, and related adverse reactions which are subject to expedited reporting, will be unblinded before submission to the Regulatory Authorities.

The overall randomization code will be broken only for reporting purposes. This will occur once all final clinical data have been entered onto the database and all data queries have been resolved, and the assignment of patients to the analysis sets has been completed.

5.7 Drug Accountability

The designated site staff is responsible for maintaining accurate study drug accountability records throughout the study in the IWRS system. The clinical research monitor will review the accountability records.

Upon receipt of study drug the site staff will accept the shipment in the IWRS system. Retained samples will be identified and segregated during initial process of accepting the shipment.

Each dispensing of study drug will be done through IWRS and recorded in the eCRF. Patients will be asked to keep all used and unused study drug containers and outer packaging (carton boxes) and return them to the designated study staff member at Visit 4. Site staff will log in all returned study medication in IWRS.

With the exception of the retained samples, the Investigator is responsible for returning all unused or partially used study drug to the Sponsor or designee and must verify that all unused or partially used drug supplies have been returned by the patient and that no remaining supplies are in the Investigator's possession.

5.8 Compliance

Patients will be instructed on proper study drug usage by designated site staff. All study drug will be self-administered by the patients. The date and time of dosing will be recorded by the patient in his or her eDiary. Comments will be recorded if there are any deviations from the planned dosing times or procedures. Compliance will be assessed separately during the Run-in Period and the Treatment Period.

5.8.1 Study Drug Compliance

Compliance with study drug will be determined by the eDiary.

- Compliance during the Run-in Period of at least 75% (based on eDiary entries) is required for a patient to qualify for randomization.
- Once randomly assigned to study drug at Visit 2, patients must take between 75% and 125%, inclusive, of planned doses to be considered in compliance with study requirements and to be included in the PPS.

Patients should complete at least 80% of the daily diary pages during the Run-in and Treatment Periods.

5.9 Previous and Concomitant Medications

Any medication the patient takes other than the study drug, including herbal and other non-traditional remedies, is considered a concomitant medication. All prior medications taken within 2 months before study entry and new or changed concomitant medications taken during the study must be recorded in the eCRF. The following information must be recorded for each medication:

- Generic name.
- Route of administration.
- Start and stop dates.
- Dosage.
- Frequency.
- Indication.

Any changes in the dosage or regimen of a concomitant medication also must be recorded.

After Visit 1, prohibited concomitant medications include the following:

- Leukotriene modifiers.
- Oral or parenteral corticosteroids.
- LABAs and SABAs (except for study-supplied rescue medication).
- Any ICS or LABA, other than (blinded) study drug.

Refer also to inclusion criterion 6 (Section 4.1) and Exclusion Criterion 7 (Section 4.2) for excluded medications.

Table 2 lists previous and concomitant medications with their required washouts prior to lung function measurements.

6 VARIABLES AND METHODS OF ASSESSMENT

Please refer to Table 1, the Schedule of Procedures for the timing of events. Methods of analysis of variables are described in Section 8.

6.1 Lung Function and Reversibility Testing

Lung function measurements will be performed at the visits specified in the Schedule of Procedures (Table 1). Compliance with concomitant medication and study drug usage is critical before lung function tests can be conducted (see Section 5.8) or lung function tests will have to be re-scheduled. Each patient must perform spirometry assessments while in the same position (either sitting or standing) at each study visit. Every attempt should be made to standardize the time of day that a patient undergoes lung function testing throughout the study. All lung function tests, except for serial spirometry, will be conducted before any administration of study drug or rescue medication.

6.1.1 Spirometry

Spirometry will be implemented and analyzed via a central spirometry facility, to ensure quality data and to minimize variability between sites.

Spirometry will be performed using standardized equipment that will be provided by a centralized spirometry service [REDACTED] that meets or exceeds the ATS/ERS joint recommendations [10]. Both absolute and percent of predicted values will be recorded. The predicted normal values will be based on the equations derived from the NHANES III dataset for adults [9]. Peak expiratory flow rate and FEV₁ will be performed to measure patient lung function.

For this study, a spirometry session is defined as a group of flow volume loops from which FEV₁ data are derived. Within each spirometry session, it is required that patients produce flow volume loops of acceptable quality, as per ATS/ERS recommendations. Repeat spirometry maneuvers may be performed as necessary, up to a maximum of 8 efforts per session. Spirometry sessions must be stopped if the patient becomes tired or breathless. From each spirometry session, the highest acceptable measurement of FEV₁ will be used for statistical analysis.

All study visits, during which spirometry is performed, should be initiated in the morning, before 11:00 am. Spirometry should be assessed at least 6 hours after the patient's last dose of study-supplied short-acting beta agonist (albuterol/salbutamol). The acceptability of the data will be reviewed by blinded over-readers provided by [REDACTED]. Standardized spirometry software will be used to assess the maneuvers and to calculate percent predicted values and percent reversibility.

At Visit 1 (screening), an initial spirometry session is performed, followed by a 30 (± 10)-minute wait period, during which 360 mcg of albuterol (400 mcg salbutamol) is administered. Next, a second spirometry session is performed to evaluate for FEV₁ reversibility (Section 6.1.2).

At Visit 2 (randomization visit), all patients will perform 3 spirometry sessions, at 60, 30, and 5 minutes pre-dose (the average of the highest acceptable FEV₁ from each session constitutes the baseline FEV₁ value). A minimum of 2 observations are required for calculation of the baseline value. Patients meeting study requirements will undergo

randomization and receive their first dose of study drug. Spirometry sessions will then be performed at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hour post-dose. Use of rescue inhaler at any point during the post-dose 12-hour spirometry will result in withdrawal of the patient from the study.

Baseline (Visit 2) FEV₁ should be $\geq 45\%$ and $\leq 85\%$ of predicted normal value and not vary by more than $\pm 20\%$ from the screening visit FEV₁ value.

At Visits 3 and 4, patients will be at the study site before 11:00 am for spirometry assessments. FEV₁ will be determined in spirometry sessions performed at 60, 30, and 5 minutes pre-dose of study drug.

6.1.2 Reversibility Testing

Airflow reversibility is not an outcome variable of this study but it is an inclusion criterion applicable to spirometry (see inclusion criterion 8, Section 4.1). Reversibility testing will be conducted at Visit 1. FEV₁ readings will be taken; then 360 mcg of albuterol (or 400 mcg salbutamol) is administered using the rescue medication provided to the patient. Thirty minutes later (± 10 minutes), 1-2 FEV₁ measurements are taken so reversibility can be assessed. For this study, FEV₁ reversibility is defined as an increase in FEV₁ (from the highest acceptable flow volume maneuver) of $\geq 15\%$ and ≥ 0.20 L. If the patient achieves $< 15\%$, but $\geq 10\%$ reversibility at Visit 1, the site may instruct the patient to hold LABA and/or ICS and return up to 7 days later for a repeat test. Only 1 repeat of the Visit 1 spirometry (to retest reversibility) is allowed per screening.

6.2 Daily eDiary Assessments

This study will use an eDiary. Patients will be provided with the eDiary at Visit 1 and will be shown how to use it. Patients will be expected to complete the eDiary at home on a daily basis and to bring it with them to every clinic visit.

During the Run-in Period and 6-week Treatment Period patients will be asked to perform the following in the order listed each day:

- Record the number of inhalations of rescue medication (albuterol/salbutamol) in eDiary card.
- Perform PEFr measurements in the morning and evening, and record the results in the eDiary.
- Inhale study drug at approximately 12 hour intervals in the morning and evening (after the PEFr measurements), and record the intake in the eDiary.

6.2.1 Daily Symptoms

Patients will record whether they have experienced any symptoms during the day or during the night in a eDiary. Twice each day, before taking any study drug, patients will answer Yes or No to the following questions:

Questions to be completed in the morning section of the eDiary:

- [REDACTED]

Questions to be completed in the evening section of the eDiary:

- [REDACTED]

6.2.2 Asthma Symptom Scores

The asthma symptom scores will be completed daily in the eDiary, as well as during Visits 2, 3, and 4.

Asthma symptom score is defined as:

- [REDACTED]

To be eligible for randomization the patient should have a documented total asthma symptom score of ≥ 1 for at least 2 days during the Run-in Period.

6.2.3 Study Drug Use

The patient must record in his or her eDiary the number of inhalations of study drug use during the Run-in Period and during the Treatment Period.

During the outpatient treatment periods, the patients will document each inhalation on their eDiary. This will be regarded as source documentation. At the beginning of each visit, the Investigator will thoroughly review the patient's eDiary entries and discuss the results with the patient. The patients will be asked if they have inhaled the study medication twice daily according to protocol. They will also be questioned about their medication washout periods. Patients will be reminded that they must inhale the study medication as instructed.

Compliance will be verified by the use of patient eDiaries (Section 5.8.1). Inhalation not documented will be considered "missed".

6.2.4 Rescue Medication Use

The patient will also record in his/her eDiary the number of inhalations of rescue medication (albuterol/salbutamol inhaler) used in each of the previous 12-hour time periods. This information will be collected by sites at each visit and entered into source documents to be kept at the site.

6.2.5 Peak Expiratory Flow Rate Measurements

Patients will be given a peak flow meter at Visit 1 for use at home to measure PEFR and will be instructed how to use it. Data from the [REDACTED] device will synchronize directly with the eDiary via Bluetooth. Three PEFR maneuvers should be performed in each session, twice daily. The highest PEFR of the 3 efforts from any session will be the one that will be recorded in the eDiary.

Morning PEFR should be recorded between 5:00 am and 10:00 am and evening PEFR between 5:00 pm and 11:00 pm. All PEFR measurements should be taken before patients take their study drug. Patients should not, whenever possible, use SABA reliever therapies for 6 hours before performing PEFR.

Patients will need to bring the peak flow meter to each clinic visit.

6.3 Adverse Events

6.3.1 Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a patient who is administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, abnormal laboratory finding temporarily associated with the use of the investigational medicinal product (IMP), whether or not related to the IMP.

Any AE that occurs after start of screening but before starting first dose of placebo will be captured as an AE but will be considered as not treatment-emergent for the purposes of data analysis.

Adverse reaction: Any untoward and unintended sign (including an abnormal laboratory finding) in a patient to an IMP which is at least possibly related to any dose administered to that patient.

A SAE is defined as any AE that:

- Results in death.
- Is life-threatening (the term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Medically important condition.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient or the patient may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Elective procedures requiring hospitalization will not be considered SAEs if they were pre-planned prior to signing the consent. However, complications of elective surgery and/or any other events that occur during the hospitalization may be considered serious or non-serious adverse events and will need to be captured according to the protocol.

Generally, study patient's visit to a hospital during study, e.g., related to an AE, not requiring overnight admission will not be regarded as hospitalization. Medical judgment should be applied on a case-by-case basis for such events, as they may meet other seriousness criteria (i.e., medically important).

A SUSAR is any adverse reaction that is classed in nature as serious, is considered associated with the use of the study drug, and which is not consistent with the available information on the medicinal product in question.

Expected versus unexpected adverse reaction: An unexpected adverse reaction is defined as a reaction which in nature or severity is not consistent with the reactions listed in the IB.

Investigator judgment should be used in deciding whether to report the signs and symptoms of worsening asthma as an AE or SAE in the eCRF. All serious asthma exacerbations occurring during the study should be recorded as an AE. Those exacerbations requiring emergency room treatment, or resulting in hospitalization or death should be recorded as a SAE (Section 6.3.3).

6.3.2 Recording Adverse Events

The clinic staff will record all AEs observed, queried, or spontaneously volunteered by the patients (regardless of seriousness or relationship to study treatment) in the appropriate section of the patient's case report form or source documents. AEs will be collected as of Visit 1 and throughout the study, including at any return clinic visits, until the end of the study.

Patients experiencing AEs (including those withdrawn from the study due to an AE) will be followed until an outcome is determined.

The following details will be recorded for AEs:

- Description of event/symptom.
- Onset date and time of event.
- End date and time of event.
- Maximum severity/intensity rated as follows:
 - Mild: Discomfort noted, but no disruption to normal daily activities.
 - Moderate: Discomfort sufficient to reduce or affect normal daily activities.
 - Severe: Inability to work or perform normal daily activities.
- Action taken with study drug noted as follows:
 - None.

- Any other action taken (such as concomitant medication, non-drug therapy, both, or none).
- Outcome of AE noted as follows:
 - Recovered/resolved.
 - Recovered/resolved with sequelae.
 - Ongoing.
 - Unknown.
 - Death.
- Causality noted as follows:
 - Unrelated: An AE which is clearly and incontrovertibly due only to extraneous causes and does not meet criteria listed under possible or probable, and is therefore not related to the use of the drug.
 - Possibly related: An AE which might be due to the use of the study medication. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s) is inconclusive. The relationship in time is reasonable; therefore the casual relationship cannot be excluded.
 - Probably related: An AE which might be due to the use of the medication. The relationship in time is suggestive (e.g., confirmed by de-challenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).
 - Related: An AE which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), and concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by de-challenge and re-challenge).

6.3.3 Follow-up of Adverse Events

All AEs will be followed up until resolution or until 30 days from the last dose, or until the Investigator is of the opinion that follow-up is no longer required.

Adverse laboratory parameters will be followed up till the values return to baseline, acceptable levels, show a tendency towards resolution, or until 30 days from the last dose, or until the Investigator is of the opinion that follow-up is no longer required.

Clinically abnormal vital signs will be followed up until the values return to baseline or until 30 days from the last dose, or until the Investigator is of the opinion that follow-up is no longer required.

6.3.4 Reporting Serious Adverse Events

Any SAE or pregnancy, whether deemed drug-related or not, must be reported by the Principal Investigator or the Principal Investigator's designee simultaneously to the Sponsor's SAE contact, [REDACTED] Medical Monitor and Clinical Trials Safety Center, Actavis Global Pharmacovigilance, and Actavis Clinical R&D, as specified in Table 3, within 24 hours after the Principal Investigator or member of the study team becomes aware of its occurrence.

The Principal Investigator or the Principal Investigator's designee must complete an SAE form (along with the study specific fax coversheet, if needed) within that 24 hour time

period. The Principal Investigator or the Principal Investigator’s designee must also enter the SAE in the appropriate AE page of the eCRF, indicating that the event is considered serious, and providing all details per the eCRF completion guidelines.

Table 3: Reporting Contacts for SAEs

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

In the event that the site is unable to complete the SAE form or eCRF entry to report the event within 24 hours of their knowledge of the event, the Investigator may report the SAE over the telephone via the SAE answering service, and then provide the completed SAE form via email/fax.

If questions arise regarding the reporting procedures or the specifics of the reporting of an event, sites may call utilizing the following number:

- [REDACTED]

Note: a “SAE Telephone Notification Form” ([REDACTED]) is utilized by the Drug Safety Associate/Specialist to capture information gathered during telephone reporting.

If the event is life-threatening or results in death, a written summary will be provided fully documenting the event, in order to permit the Sponsor to file a report which satisfies regulatory guidelines, within 3 calendar days.

SAE reporting will be handled according to local regulatory requirements. Any follow-up information will be reported to the Sponsor’s SAE contacts, IRB/IEC, and Regulatory Authorities according to local regulatory requirements.

The minimum criteria for an SAE report are:

- A suspected investigational drug.
- An identifiable patient.
- An AE assessed as serious.
- An identifiable reporting source.

The Principal Investigator or the Principal Investigator’s designee must include the following information:

- Principal Investigator name and site number (if applicable).
- Patient ID number.
- Patient initials and date of birth.
- Patient demographics.
- Clinical event:
 - Description.
 - Date of onset.
 - Intensity.
 - Treatment (including hospitalization).
 - Relationship to study drug.
 - Action taken regarding study drug.

If the AE was fatal, the report should include:

- Cause of death (whether or not the death was related to study drug).
- Autopsy findings (if available).
- Death certificate.

The Principal Investigator or the Principal Investigator's designee will provide follow-up information as it becomes available. The follow-up report will contain a full description of the event and any sequelae. Patients who have had an SAE must be followed clinically until all parameters (including laboratory) have either returned to normal or are stabilized. Once follow-up information becomes available, it must be reported to the contacts specified in Table 3, as necessary, within **24 hours** of receipt.

Further details regarding the SAE reporting process will be documented in the Safety Management Plan.

6.3.5 Removal of Patients from Study Due to Adverse Events

Patients will be advised they are free to withdraw from the study at any time. Over the course of the study, the Investigator(s) and/or the Sponsor may discontinue participation of any patient from the study in the case of unnecessary risk, adverse drug events, or noncompliance. When a patient withdraws from the study, all safety data normally required at the end of the study will be obtained, if possible.

6.3.6 Termination of Study Due to Adverse Events

If, in the opinion of the Investigators, Sponsor, or the IRB/IEC, the incidence and severity of AEs outweighs the benefit of continuing the study, the study may be terminated. In the event this course of action is to be pursued, the Investigators will make every attempt to communicate with the Sponsor prior to the decision to develop a complete plan of action and to assess outcomes.

6.3.7 Suspected Unexpected Serious Adverse Reactions

Any SUSAR has additional reporting requirements, as described below.

- If the SUSAR is fatal or life-threatening, associated with the use of the study drug, and unexpected, Regulatory Authorities and IECs will be notified within 7 calendar

days after [REDACTED] learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information should be reported within an additional 8 days (15 days total).

- If the SUSAR is not fatal or life-threatening but is otherwise serious, associated with the use of the study drug, and unexpected, Regulatory Authorities and IECs will be notified within 15 calendar days after [REDACTED] learns of the event.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of patients. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the Regulatory Authorities and IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

6.3.8 Pregnancy

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered a SAE.

Pregnant patients (confirmed positive pregnancy test result at any time from the time of study drug administration until the end of the study) must be withdrawn from the study (Section 4.4).

All pregnancies must be reported to [REDACTED]/Sponsor on the initial pregnancy report form within 24 hours after discovery by the Investigator or clinical staff, as described in Section 6.3.4.

The Investigator must follow-up and document the course and the outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished.

All outcomes of pregnancy (including voluntary or spontaneous termination, details of birth, presence or absence of congenital abnormalities, birth defects, maternal and neonatal complications, and possible relationship to study drug) must be reported by the Investigator to [REDACTED]/Sponsor on the pregnancy outcome report form within 30 days after he or she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy (including SAEs occurring after last administration of study drug) must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

If a female partner of a male study patient who has been exposed to the study drug becomes pregnant, the pregnancy and outcome of pregnancy should be monitored.

The IEC/IRB and Regulatory Authorities will be informed of the pregnancy in accordance with local laws and regulations.

6.4 Laboratory Variables

Blood and urine samples will be collected at the visits presented in the Schedule of Procedures (Table 1).

A central laboratory will perform the routine analysis of blood and urine specimens, as identified in the List of Study Personnel. Detailed instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study.

Laboratory results will not be entered into the eCRF. However, the date and time of sampling will be recorded.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date and time of sample collection will be recorded on the eCRF.

Abnormalities of safety laboratory parameters should be reported as an AE if they are considered to be clinically significant. If an abnormal safety laboratory value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated abnormal laboratory result should be considered additional information. The reporting of safety laboratory abnormalities as both laboratory findings and AEs should be avoided. Abnormalities of safety laboratory parameters that are part of the disease profile prior to study treatment do not need to be reported as an AE.

Approximately 32 mL of blood will be collected during the study (excluding any unscheduled/repeat samples).

The following laboratory variables will be determined (Table 4).

Table 4: Laboratory Assessments

Test Group	Analyte/Component
Hematology:	red blood cell count red cell distribution width hemoglobin hematocrit mean cell hemoglobin concentration white blood cell count and differential mean cell volume mean cell hemoglobin platelet count
Urinalysis:	protein glucose specific gravity ketone bilirubin pH blood
Clinical chemistry:	protein albumin total bilirubin alanine transaminase aspartate transaminase glucose sodium potassium calcium bicarbonate blood urea nitrogen/urea creatinine alkaline phosphatase
Serum pregnancy test (β-HCG):	In females of childbearing potential only.
Urine pregnancy test:	In females of childbearing potential only.
Urine alcohol/drug/cotinine test:	Amphetamines (stimulants), MDMA (ecstasy), barbiturates, benzodiazepines, cannabinoids/tetrahydrocannabinol (THC)/marijuana, cocaine, opiates, alcohol, and cotinine.

6.5 Vital Signs

Vital signs (blood pressure, pulse, respiratory rate, and body temperature) will be measured in accordance with the Schedule of Procedures (Table 1). Vital signs will be measured after at least 10 minutes rest in supine position. On Visits 2, 3, and 4, measurements will be done in the morning prior to inhalation, and a patient will not be administered if his/her blood pressure or pulse is deemed as clinically significant abnormal by the Investigator.

Vital signs need only be taken once during each visit.

6.6 Electrocardiograms

Standard 12-lead ECGs will be performed in accordance with the Schedule of Procedures (Table 1).

12-lead ECG to be measured after at least 10 minutes rest in supine position and the patient should be motionless during the recording.

The ECG may be taken before any blood sampling, or 15 minutes after. Where possible, the patient should be examined using the same ECG machine throughout the study. ECGs will be recorded digitally and read by the Investigator or the qualified ECG technician for recording in the eCRF. A duplicate copy of the ECG reading will be anonymized and maintained with the source documents. Care should be taken to assure proper lead placement and quality ECG recordings.

Any clinically significant finding observed on the ECG (e.g., QTc [Bazett's] >500 ms) at Visit 4, will be record as an AE by the Investigator.

6.7 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Procedures (Table 1).

The examination will include an assessment of the patient's general appearance (including evaluation of extremities, eyes, nose, mouth/throat/neck, and thyroid), measurement of height and weight (without shoes), and a review of body systems (dermatologic, lymphatic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurologic, and psychiatric).

7 STUDY CONDUCT

The schedule, as outlined in Table 1, consists of a Run-in Period and Treatment Period. A brief summary of the overall conduct is presented below.

7.1 Procedures by Visit

All times should be recorded using the 24-hour clock (e.g., 23:20, not 11:20 pm).

All visits must be initiated before 11:00 am, but must be scheduled to allow completion of the relevant assessments prior to taking study drug at the patient's regular morning time.

7.1.1 Informed Consent

Informed consent/assent may be signed up to 14 days prior to Visit 1. Written informed consent/assent must be obtained prior to any study-related procedure which includes medication washout and restrictions.

7.1.2 Screening (Visit 1)

A summary of the procedures during Visit 1 is below:

- Check written informed consent/assent has been obtained.
- Verify conformance with entry criteria.
- Record medical history (any previous and concomitant diseases occurring before screening).
- Record asthma history (include the confirmation of asthma diagnosis and date of diagnosis in addition to documentation of current asthma medication).
- Record demographic information (age, sex, ethnic origin, race, height, weight, BMI).
- Record baseline characteristics (general medical history, smoking history).
- Drug/alcohol/cotinine screen.
- Record concomitant medication use, including current asthma therapies (previous and concomitant medication will be documented as described in Section 5.9).
- Perform physical examination.
- Obtain vital signs.
- Perform 12-lead ECG.
- Obtain blood and urine samples for clinical laboratory tests.
- Serum pregnancy test (for females of childbearing potential).
- Patient training with the [REDACTED] [REDACTED].
- Perform spirometry and reversibility measurements (refer to Section 6.1).
- Review use of eDiary and daily compliance requirements and dispense eDiary and PEFR device.
- Instruct patient on administration of Run-in study drug (refer to Section 5.3).
- Study staff dispenses study drug (i.e., placebo inhaler) and rescue medication (albuterol/salbutamol) for use throughout the study.

- AE recording.
- If a patient is deemed to be suitable to enter the Run-in Period, the first dose of placebo medication will be inhaled at the study site at Visit 1, and the correct inhalation technique will be reinforced.

7.1.3 Open Placebo Run-in Period

Following screening, eligible patients will begin a placebo Run-in Period of at least 14 days in duration, but not longer than 21 days to wash out any pre-study corticosteroids or long-acting bronchodilators, and to establish FEV₁ baseline values. Open-label placebo medication will be inhaled during the Run-in Period.

During the Run-in Period patients will be asked to complete the eDiary daily, as instructed (Section 6.2). Patients will perform PEFr measurements and inhale placebo medication at approximately 12 hour intervals.

7.1.4 Treatment Period

Patients will take test, reference, or placebo at approximately 12-hour intervals. At the beginning of each visit, the Investigator will thoroughly review the patient's eDiary entries and discuss the results with the patient. The patients will be asked about their medication washouts and whether they have experienced any unusual symptoms or medical problems since the last visit. Patients will be reminded that they must inhale the study drug as instructed. Patients will be instructed to withhold the study drug and not perform morning PEFr measurements until they arrive at the clinic on the morning of each visit.

During the 6-week Treatment Period patients will be asked to complete the eDiary daily, as instructed (Section 6.2). Patients will perform PEFr measurements and inhale study drug at approximately 12 hour intervals.

7.1.4.1 Visit 2 (Randomization)

Randomized treatment should begin within 14 days (maximum 21 days) of starting the placebo Run-in Period. Patients who remain eligible will be randomized into either the test, reference, or placebo treatment group.

The following will be performed during Visit 2:

- Collect used and unused study drug.
- Review eDiary from Run-in Period, and check compliance.
- Recheck conformance with inclusion/exclusion criteria.
- Concomitant medications.
- Contact IWRS for randomization.
- Vital signs.
- Asthma symptom score.
- Spirometry (60, 30, and 5 minutes pre-dose). FEV₁ must be in the range of $\geq 45\%$ and $\leq 85\%$ of the predicted value.
- Inhalation of first dose of study drug under supervision.

- Spirometry (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose).
- Dispense study drug and eDiary.
- Dispense additional rescue medication, if necessary.
- Provide additional inhalation and/or eDiary training, as relevant.
- AE recording.
- Urine pregnancy test (for females of childbearing potential).

7.1.4.2 Visit 3

Visit 3 will occur at the end of the third treatment week (treatment day 21 ± 7 days)

The following will be performed during Visit 3:

- Collect used and unused study drug.
- Review eDiary and check compliance.
- Concomitant medications.
- Vital signs.
- Asthma symptom score.
- Spirometry (60, 30, and 5 minutes pre-dose).
- Inhalation of study drug under supervision.
- Dispense study drug and eDiary.
- Dispense additional rescue medication, if necessary.
- AE recording.
- Urine pregnancy test (for females of childbearing potential).

Note: The same eDiary devices used in placebo run-in and Visit 2 will be returned to the patient.

7.1.4.3 Visit 4

Visit 4 will occur at the end of the sixth treatment week (treatment day 42 + a time window of +7 days).

The following will be performed during Visit 4:

- Collect used and unused study drug.
- Review eDiary and check compliance.
- Concomitant medications.
- Physical examination.
- Vital signs.
- Asthma symptom score.
- 12-lead ECG.
- Samples for clinical laboratory investigations.
- Serum pregnancy test (for females of childbearing potential).
- Spirometry (60, 30, and 5 minutes pre-dose).

- The last dose of study drug will be inhaled.
- Inhaler and eDiary will be collected.
- AE recording.

The patient will be reminded to report any adverse experiences that occur within 30 days after the last visit.

7.1.5 Early Termination Visit

If a patient discontinues the study prematurely, he/she will be invited to undergo an early termination visit with the same procedures as on Visit 4, except there is no inhalation of the study drug. More specifically, a series of at least 3 spirometric measurements will be obtained in the morning with an interval of approximately 20 minutes in between. A medical follow-up examination including physical examination, blood pressure, pulse, ECG, and clinical laboratory investigation will be done.

The patient will be reminded to report any adverse experiences that occur within 30 days after the last visit.

8 STATISTICAL METHODS

Before database lock, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses as outlined in the following subsections. Any deviations from the planned analyses will be described and justified in the final clinical study report.

8.1 Study Patients

8.1.1 Disposition of Patients

The assignment of patients to analysis populations will be listed and summarized by treatment. The tabulation will include the following information:

- Number (n) of patients receiving at least 1 dose of randomized study drug.
- Number and percentage of patients completing the study.
- Number and percentage of patients who were withdrawn (including reasons for withdrawal).
- Number and percentage of patients in each of the analysis sets.

In addition, the number of patients enrolled, randomized, and completed will be presented by treatment and overall and by study site, and will include the number of patients withdrawn and the reasons for withdrawal.

A listing of withdrawals from the study will be presented, including date of discontinuation and primary reason.

8.1.2 Protocol Deviations

Deviations from the protocol will be assessed as “minor” or “major” in conjunction with the Sponsor during a Blinded Data Review Meeting (BDRM). Major deviations from the protocol will lead to the exclusion of patients from the PPS. Deviations will be defined before database hard lock and unblinding. Major deviations will include the following:

- Violation of inclusion and/or exclusion criteria.
- Non-compliance with the dosing schedule (i.e., patients for whom compliance during the Treatment Period was not between 75% and 125%).
- Missing data for the primary endpoints.
- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoints.
- The treatment blind is broken for a patient. (*Note: patients will not be withdrawn from the study*).

Further details will be described in the SAP.

8.1.3 Analysis Sets

<u>Analysis Sets</u>	<u>Definition</u>
Enrolled Set (ENS):	All patients who provided informed consent/assent.
Run-in Set (RiN):	All patients who enter the Run-in Period.
Modified Intent-To-Treat (mITT) set	All randomized patients who receive treatment will be included. Patients will be included in the analysis as randomized.
Per-Protocol Set (PPS):	All patients included in the mITT set who have between 75% and 125% compliance with the dosing schedule in the Treatment Period, and had no major protocol deviations that are considered to have an impact on the analysis of the primary endpoints. The PPS will be defined before database lock and unblinding during the BDRM.
Safety Analysis Set (SAF):	The SAF includes all randomized patients who receive treatment, classified by actual treatment received.

The analysis of the primary endpoints for the assessment of bioequivalence will be based on the PPS. The assessment of assay sensitivity will be based on the mITT set. All safety analyses will be based on the SAF.

8.2 General Considerations

Data will be summarized by study period, treatment and time point, as applicable. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized using number of patients, frequency, and percentages. Patient listings will include all study data. All statistical tests will be 2-sided and will be performed at the 5% level of significance, unless otherwise specified.

Statistical analyses will be performed using SAS (SAS Institute Inc., Cary, NC, US) Version 9.1.3 or higher unless otherwise specified.

8.2.1 Missing Data and Data Conventions:

Conventions for data analysis and missing data will be provided in the SAP.

8.3 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographic data characteristics (height, weight, age, sex, race, BMI, and ethnic origin) will be listed by patient and summarized by treatment and for the overall study population.

Medical history data will be listed by patient and summarized by treatment. All medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

Asthma history will be listed for each patient including the confirmation and date of diagnosis.

Smoking history, history of drug and alcohol abuse, and compliance with inclusion or exclusion criteria will be listed for each patient.

8.4 Lung Function Testing/Spirometry

The results of the spirometry measurements (including reversibility testing) on Day -14 and Day 1 will be listed for each patient including the FEV₁, FVC, and PEF_R measurements (absolute values and percentage of predicted values). For the reversibility testing, both the absolute measurements and percentage change after inhaled albuterol/salbutamol (or equivalent) will be presented.

8.5 Rescue Medications, Previous and Concomitant Medications

Rescue medications, prior medications, and concomitant medications will be coded according to the World Health Organization – Drug Reference List (WHO-DRL) and the Anatomical Therapeutic Chemical (ATC) classification system. Prior medications are defined as those taken before the first dose of randomized study drug on Day 1 (i.e., start and end date before the first dose of randomized study drug). Concomitant medications are defined as those taken at the time of or after the first dose of randomized study drug. Any medications that were started before the first dose of randomized study drug on Day 1 but continued after dosing will be considered a concomitant medication.

8.6 Treatment Compliance

Compliance with treatment will be calculated separately during the Run-in Period and during the Treatment Period.

Compliance will be calculated as:

Study drug compliance (%) = 

For patients who withdraw before completing the Treatment Period, compliance will be calculated based on the number of planned doses up until the time of withdrawal. Further details will be provided in the SAP.

8.7 Analysis of Primary Endpoints

For this pivotal study, equivalence will be based on the test/reference (T/R) ratio for the 2 co-primary endpoints. The 90% confidence intervals (CI) for both T/R ratios for the primary endpoints should fall within the limits of 80.00-125.00%.

A separate analysis of covariance (ANCOVA) model will be fit to each of the primary endpoints. The model will contain a main effect for treatment arm (one degree of freedom [DF]) and center. The baseline FEV₁ will be included as a covariate. The corresponding 90% CIs for the (T/R) ratios will be calculated using Fieller's theorem.

Equivalence analyses will be done on the PPS. Analysis of study sensitivity will be done on the mITT set.

8.7.1 Analysis of Bioequivalence

The co-primary endpoints are:

- Baseline-adjusted FEV₁ AUC₀₋₁₂ on the first day of the Treatment Period (Visit 2, Day 1).
- Baseline-adjusted pre-dose FEV₁, calculated as the mean of the 4 values measured in the morning before dosing on the last day of the Treatment Period (Visit 4, Day 42).

The FEV₁ baseline is defined as the average of 4 (at least 2) pre-dose FEV₁ values obtained at Visit 2.

The results of the serial FEV₁ measurements on Day 1 (absolute values and baseline-corrected values) will be listed by patient and summarized by treatment. Figures will be presented showing the mean absolute and baseline-corrected measurements versus time, by treatment.

Details regarding the calculations and handling of missing data will be described in the SAP.

The average FEV₁ on the last day of randomized treatment (Day 42) will be listed by patient and summarized by treatment for both absolute values and changes from baseline values.

The analysis of bioequivalence will be performed as described in Section 8.7.

In order to demonstrate bioequivalence, the 90% CI for the ratio of means (test versus reference) for both primary endpoints must fall between 80.00% and 125.00%.

Primary analyses will be done for the PPS. Actual values without the logarithms will be used in the models.

8.7.2 Analysis of Assay Sensitivity

To ensure adequate study sensitivity, the test and reference products should both be statistically superior in terms of differences to placebo ($p < 0.05$, 2-sided) with regard to the study primary endpoints. Superiority will be assessed using a similar ANCOVA model as described above, for both pairs of compared treatments. If adequate sensitivity cannot be demonstrated, bioequivalence of test and reference products cannot be concluded.

Any missing data (as a result of patient withdrawal or discontinuation) for baseline-adjusted FEV₁ at Day 42 will be imputed as described in the SAP.

8.8 Safety Analyses

The safety data will be based on the SAF. A descriptive analysis will be conducted.

8.8.1 Adverse Events

All AEs will be coded using MedDRA.

All AEs will be listed for each patient. Separate listings will be presented for AEs leading to discontinuation and SAEs.

A treatment-emergent AE (TEAE) is defined as an AE occurring at the time of or after the first dose of placebo study drug during the Run-in Period. All TEAEs will be assigned to one of the following study periods for the purposes of the tabulations:

Run-in Period: All TEAEs with onset at the time of or after the first dose of placebo study drug (Day -14) during the Run-in Period until the time of the first dose of randomized study drug (Day 1)

Treatment Period: All TEAEs with onset at the time of or after the first dose of randomized study drug (Day 1) during the Treatment Period

AEs with missing start and/or end dates and/or times (if applicable) will be handled as described in the SAP.

An overview of all TEAEs (N, incidence) will be presented by treatment and study period. The overview will include the following:

- Number and percentage of patients with TEAEs.
- Number and percentage of patients with drug-related TEAEs.
- Number and percentage of patients with treatment-emergent SAEs.
- Number and percentage of patients with TEAEs leading to permanent discontinuation of study drug.
- Number and percentage of patients with TEAEs leading to death.

Summaries of TEAEs (N, incidence) will be presented by treatment, system organ class (SOC), and preferred term (PT) for the following:

- All TEAEs.
- Serious treatment-emergent AEs.
- Drug-related TEAEs.
- TEAEs leading to permanent discontinuation of study drug.

Additional summaries will be presented by severity and by causality.

8.8.2 Safety Laboratory Tests, Vital Signs, and ECGs

Laboratory safety assessment (i.e., clinical chemistry and hematology), vital signs, and ECGs will be assessed by Investigators for the presence of any findings that meet the description of an AE. Laboratory test results will not be listed or summarized. Vital signs and ECGs will be tabulated and listed. Any positive pregnancy test results will be documented on pregnancy report forms.

8.8.3 Physical Examination

Physical examination results will be listed by patient and body system.

8.8.4 Daily Diary Questions

The PEFr entries from the patients' diaries will be listed for each patient for both morning and evening measurements obtained during the Run-in Period and the Treatment Period.

8.9 Other Analyses

The symptom scores and other variables will be collected descriptively.

8.10 Interim Analyses

No formal interim analysis with statistical stopping rules will be undertaken.

To check the assumptions which underlie the original design and sample size calculation,

[REDACTED]

8.11 Determination of Sample Size

[REDACTED] Approximately
1130 patients will be randomized

[REDACTED]

[REDACTED]

[REDACTED]							
[REDACTED]							
[REDACTED]							

[REDACTED]

The sample sizes above are sufficient to demonstrate:

- Equivalence between the test vs. RLD such that the 90% CI for the test vs RLD Ratio lies completely with 0.8 to 1.25
 - The test and RLD are superior to placebo at the 2 sided 5% significance level
- Estimates of sample size were calculated under the following assumptions for equivalence:

[REDACTED]

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The study site will implement and maintain quality control and quality assurance procedures to insure that the study is conducted, and that the data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory documents.

The Sponsor may conduct monitoring and/or audit visits to the CRO study site to verify adherence to the study protocol, the protection of the rights and well-being of the patients and the accuracy and completeness of reported study data recorded on the source documentation.

9.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the eCRF.

9.2 Case Report Forms and Source Documentation

All source documents from which eCRF entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments and ECG. Data that will be entered directly into the eCRF (i.e., for which there is no prior written or electronic record of data, such as Quality of Life assessments) are considered to be source data.

The original eCRF entries for each patient may be checked against source documents at the study site by the [REDACTED] site monitor.

After review by the site monitor, completed eCRF entries will be uploaded and forwarded to the CRO. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the eCRF.

9.2.1 Data Collection

The Investigators (and appropriately authorized staff) will be given access to an online web-based eCRF system which is 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the eCRF system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the eCRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved online. All discrepancies will be solved online directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data

Data about all study drug dispensed to the patient and any dosage changes will be tracked on the eCRF.

Spirometry and eDiary data will be transferred directly from the spirometer and eDiary, respectively, to the central spirometry laboratory (██████████) and are not captured in the eCRF.

9.3 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures ██████████ and the Sponsor of the necessary support at all times.

Sites will be able to download and print copies of the spirometry and eDiary results. Access to spirometry and eDiary source data must be provided via the ██████████ system.

9.4 Data Processing

Patient data (except spirometry, eDiary, and central laboratory data) will be entered by site personnel into the eCRF (as detailed in Section 9.2.1).

The data review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated on the basis of signed corrections.

External electronic data (e.g., spirometry data, eDiary data, laboratory data) will be transferred from the vendor and loaded into a validated electronic database. Details of data transfer will be provided in the spirometry and laboratory manuals. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

Previous and concomitant medications will be coded using the WHO-DRL), which employs the ATC classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

Previous and concomitant diseases as well as AEs will be coded with MedDRA.

The versions of the coding dictionaries will be provided in the clinical study report.

9.5 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the GCP guidelines of the ICH, the Code of Federal Regulations, and of the Declaration of Helsinki and all amendments. The study also will be carried out in keeping with local legal requirements.

9.7 Informed Consent

A copy of the study specific consent document to be used (prepared in compliance with FDA and European regulations and guidelines and in accordance with ICH GCP E6) will be reviewed by the IRB/IEC and written approval obtained prior to the start of the study.

Before each patient is admitted to the study, written informed consent will be obtained from the patient (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. The consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid

consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF system.

For patients who are below the legal age to provide informed consent (per specific country requirements), their legal guardian will complete the informed consent form, and the patient will complete an assent form.

For centers in Germany, if applicable: According to the German Medicines Act, under-age patients must personally provide informed consent (in addition to their legal representatives) provided they are able to understand the information given to him/her in this study.

For centers in EU, if applicable: The explicit wish of a minor, or mentally incapacitated adult, who is capable of forming an opinion and assessing the study information, to refuse participation in or to be withdrawn from the study at any time will be respected by the Investigator.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US, following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.9 Duration of the Study

For an individual patient, the planned duration of the study will be up to 8 weeks (including 14 days [2 weeks] of placebo Run-in and 42 days [6 weeks] of randomized treatment).

The study will close when all patients have completed Visit 4 (or Early Termination Visit in case of early withdrawal).

9.10 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be

terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure to enroll patients at an acceptable rate.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

9.11 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to [REDACTED] by their patient number, initials and/or birth date, not by name. Documents not to be submitted to [REDACTED] that identify the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator. An appropriate data privacy statement should be included in the informed consent document.

9.12 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties— Regulatory Authorities, Investigators, and IRB/IECs.

A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent.

9.12.1 Institutional Review Board/Independent Ethics Committee

The Investigator(s) agree to provide the IRB/IEC with all appropriate material, including a copy of the protocol, consent document, and advertising text (if study specific advertising is used). The study will not be initiated without written IRB/IEC approval of the research plan and consent document. Copies of the IRB/IEC approval will be forwarded to the Sponsor. The Investigator(s) will provide appropriate reports on the progress of this study to the IRB/IEC and Sponsor in accordance with applicable government and/or Institute regulations and in agreement with Sponsor policy. The IRB/IEC will be informed of any modifications of the protocol or consent document.

9.12.2 Investigator's Statement

The Investigator must agree to conduct the trial as outlined in the approved protocol and in accordance with the Sponsor's guidelines and all applicable federal government codes, acts and regulations, and ICH GCP (E6).

9.13 Publication Policy

By signing the clinical study protocol, the Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

After study completion, a final integrated report covering clinical and statistical aspects of the study will be prepared (according to the ICH E3 guideline). As required by the applicable regulatory requirements, the clinical study report will be signed by the Sponsor's responsible medical officer as well as the coordinating Investigator (if applicable).

An Investigator or the CRO shall not publish, or present for publication any articles or papers or make any presentations, nor assist any other person in publishing any articles or papers or making any presentations, or making any public declaration relating or referring to the clinical study, the results of the clinical study, in whole or in part, without the prior written consent of the Sponsor.

10 REFERENCE LIST

- 1 Global Strategy for Asthma Management and Prevention. The GINA Report, updated 2015, available on www.ginasthma.org
- 2 World Health Organization (WHO). Asthma fact sheet; Number 307. <http://www.who.int/mediacentre/factsheets/fs307/en/>. Updated November 2013. Accessed March 7, 2014.
- 3 [REDACTED]
- 4 [REDACTED]
- 5 [REDACTED]
- 6 Prescribing Information for Symbicort® Rev 5/12. <https://www.symbicorttouchpoints.com/asthma-therapy.html>
- 7 U.S. Food and Drug Administration (FDA) Draft Guidance on Budesonide; Formoterol fumarate dihydrate. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM452690.pdf>
- 8 National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007. U.S. Department of Health and Human Services, National Institutes of Health. National Heart, Lung, and Blood Institute. 2007, Publication No. 07-4051. http://www.nhlbi.nih.gov/guidelines/asthma/01_front.pdf
- 9 [REDACTED]
- [REDACTED]

11.2 Guide to Lower Limits of BMI in Adolescents

Age	5th Percentile BMI (approximate)
12	15
13	15.5
14	16
15	16.5
16	17
17	17.5
18	18.25