3M Health Care Ltd

CSP-07-000034

A RANDOMIZED, SINGLE-BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED, MULTIDOSE STUDY COMPARING THE THERAPEUTIC EQUIVALENCE OF A 3M INHALER AND A SYMBICORT® REFERENCE INHALER, EACH DELIVERING BUDESONIDE/FORMOTEROL FUMARATE (80 µg/4.5 µg) IN ADULT SUBJECTS WITH ASTHMA

Statistical Analysis Plan, Final Version 2.0
23 Mar 2018

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List of Abbreviations

ADaM	Analysis Data Model (ADaM)
AE	Adverse event
AIC	Akaike information criterion
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
AUC	Area Under the Curve
AUC_{0-12}	Area Under the Concentration-Time Curve from Zero up to 12 Hours
BMI	Body Mass Index
BP	Blood pressure
CI	Confidence Interval
CMD	Concomitant Medication
CRF	Case report form
CTMS	Clinical Trial Management System
CT	Clinical Trial
CV	Coefficient of Variation
DBL	Database Lock
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
xxx	
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
GINA	Global Initiative for Asthma
ICF	Informed Consent Form
ICS	Inhaled corticosteroid
xxx	
LABA	Long Acting β_2 Agonist
LS	Least Squares
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
NAEPP	National Asthma Education and Prevention Program
xxx	
PD	Protocol Deviation
xxx	
pMDI	Pressurized Metered-Dose Inhaler
PFT	Pulmonary Function Test
pMDI	Pressurized Metered Dose Inhaler
PPS	Per-Protocol Set
PT	Preferred Term
SABA	Short Acting β_2 Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SB	Single-Blind
SD	Standard Deviation
SDTM	Standard Data Tabulation Model
SID	Subject Identification
SOC	System organ class
SS	Sum of Squares
USA	United States of America
WHO	World Health Organization

1. Introduction

Asthma is a common respiratory disease. It is characterized by chronic airway inflammation leading to airflow obstruction with symptoms such as breathlessness, cough, impairment of physical activity, and potentially death. Prevalence data in the United States between 2001 and 2010 indicated an overall increase in asthma during the period [Akinbami, 2012], and by 2014, there were 24 million people with asthma [CDC, 2016].

Inhaled corticosteroids have been widely used as a safe and effective anti-inflammatory therapy for the treatment of persistent asthma for many years. Inhaled corticosteroids are recommended as the maintenance treatment of choice in treatment guidelines (ie, Global Initiative for Asthma [GINA] and the National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program [NAEPP]) in all but patients with mild intermittent asthma whose symptoms are adequately maintained on short-acting β2 agonists (SABAs) alone.

Long-acting β agonists (LABAs) have also been widely used as safe and effective bronchodilator therapy for the treatment of persistent asthma for many years, and they are also recommended as a maintenance therapy in conjunction with inhaled corticosteroids xxx for patients with moderate to severe asthma who remain symptomatic despite low-dose inhaled corticosteroids and SABAs (as needed).

Symbicort® is approved by the US Food and Drug Administration (FDA) as a combination product containing a corticosteroid and a LABA and is indicated for the treatment of asthma patients 12 years of age and older and for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including chronic bronchitis and emphysema. It is not indicated for the relief of acute bronchospasm. It is available as a pressurized metered-dose inhaler (pMDI) containing a combination of budesonide (80 or 160 µg) and formoterol (4.5 µg) as an inhalation aerosol and is administered as 2 inhalations twice daily (morning and evening, approximately 12 hours apart) [Symbicort, 2016].

3M Health Care Ltd (3M) is developing a drug product (3M Inhaler) that is a pMDI containing a combination of budesonide (80 µg) and formoterol (4.5 µg) as an inhalation aerosol. The 3M Inhaler is expected to be equivalent to the currently available Symbicort (referred to in this protocol as Symbicort Reference Inhaler) in terms of reproducibility of delivery of both emitted and respirable dose of medication. The 3M Inhaler is being developed as a generic equivalent of the Symbicort Reference Inhaler in order to provide a choice for patients, prescribers, and payers.

2. Objectives

CSP-07-000034 will investigate the effect of pMDI on FEV_1 AUC_{0-12} after the first dose on Day 1 of the study and on FEV_1 at the End-of-Treatment Visit (Week 6) to assess the equivalence of the 3M Inhaler compared with a Symbicort Reference Inhaler in delivering budesonide/formoterol fumarate (80 µg/4.5 µg).

The primary objectives of this study are as follows:

- To demonstrate the equivalence of the 3M Inhaler compared with a Symbicort Reference Inhaler in delivering budesonide/formoterol fumarate (80 µg/4.5 µg)

- To demonstrate the superiority of the 3M Inhaler and the Symbicort Reference Inhaler compared with placebo.

The safety objectives of this study are as follows:

- To assess the safety of the 3M Inhaler compared with a Symbicort Reference Inhaler in delivering budesonide/formoterol fumarate (80 µg/4.5 µg) and compared with placebo.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a randomized, single-blind, parallel-group, placebo-controlled, multidose study designed to evaluate local equivalence of 3M Inhaler vs. Symbicort Reference Inhaler. Specifically, equivalence of 3M Inhaler budesonide/formoterol fumarate (80 µg/4.5 µg) to Symbicort Reference Inhaler budesonide/formoterol fumarate (80 µg/4.5 µg) will be evaluated. Assay sensitivity analysis is also planned by comparing 3M Inhaler and Symbicort Reference Inhaler to Placebo inhalers. The co-primary endpoints for these analyses are AUC_{0-12} of the change from baseline in FEV_1 at Day 1 and change from baseline in trough FEV_1 (L) at the End-of-Treatment Visit (Week 6).

Approximately 1470 adult subjects with asthma will be enrolled at approximately 100 study centers in the United States. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria. Each subject is expected to be in the study for approximately 8 to 10 weeks, which includes screening, a 2-week placebo run-in period, and a 6-week treatment period. It is expected that the total duration of the study will be approximately 9 to 12 months.

During the screening visit, subjects will be given instructions on how to use the placebo run-in period inhaler, and subjects will be informed that compliance to the placebo run-in period inhaler schedule will be checked at the baseline visit. The first placebo run-in dose will be administered at the study center at the end of the screening visit. Compliance should be 75-125% of per protocol dosing for subjects to be eligible to enter the single-blind treatment phase of the study; timing of dosing will be captured in a subject diary and assessment of dose counters on inhalers will be made at study visits. The primary assessment of compliance will be the dose counter.
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The study will incorporate:

- A Screening visit (approximately 14-21 days prior to randomization), followed by a 14-21 days placebo run-in period.

- A 6-week study treatment period, encompassing the following visits:

    - Baseline Visit: Day 1 (Baseline)
    - The first telephone contact: Day 14 ± 2 days (Week 2)
    - The second telephone contact: Day 28 ± 2 days (Week 4)
    - End-of-Treatment Visit: Day 42 ± 2 days (Week 6).

Screening to discharge will be approximately 2 months in duration.

At the baseline visit, subjects will be given 2 inhalers of study medication, clearly labeled as Inhaler 1 and Inhaler 2, based on their randomized treatment (3M Inhaler, Symbicort Reference Inhaler, or placebo). Subjects will use Inhaler 1 until the Week 4 telephone call visit. At the Week 4 telephone visit, subjects will be instructed to switch to Inhaler 2 beginning with the evening dose on the day of the telephone visit and use that inhaler for the remainder of the study.

The first dose of randomized treatment will be administered in the clinic on Day 1 with pulmonary function tests being performed up to 12 hours post dose. The FEV_1 measurements from this visit are key to assessing the FEV_1 AUC_{0-12} primary endpoint. The visit to assess change from baseline to the end-of-treatment in FEV_1 is on the End-of-Treatment Visit (Week 6).

A complete overview of study activities is shown in the schedule of study procedures included in Appendix 13.1.

3.2. Study Endpoints

The following are the co-primary endpoints:

- Area under the concentration-time curve of the change from baseline in forced expiratory volume in 1 second (FEV_1) from zero up to 12 hours (AUC_{0-12}) at Day 1
- Change from baseline in trough FEV_1 measured in the morning at the End-of-Treatment Visit (Week 6)

Safety will be evaluated by assessing number (percent), severity, and relatedness of AEs and SAEs between treatment groups.

3.3. Treatments

The following treatments will be administered during the study:

- Run-in placebo via placebo inhaler (over the 2-week placebo run-in period, 2 inhalations

twice daily)

- Budesonide/formoterol fumarate (80 µg/4.5 µg) via the 3M Inhaler (over the 6-week treatment period, 2 inhalations twice daily)
- Budesonide/formoterol fumarate (80 µg/4.5 µg) via the Symbicort Reference Inhaler (over the 6-week treatment period, 2 inhalations twice daily)
- Placebo via a placebo inhaler (over the 6-week treatment period, 2 inhalations twice daily)

The 3M Inhaler is a pMDI containing a combination of budesonide (80 µg) and formoterol (4.5 µg) as an inhalation aerosol. The 3M Inhaler also contains the following inactive excipients: xxx.

The Symbicort Reference Inhaler is a pMDI containing a combination of budesonide (80 µg) and formoterol (4.5 µg) as an inhalation aerosol. The Symbicort Reference Inhaler contains the following inactive excipients: xxx. The placebo inhaler is identical in appearance to the 3M Inhaler. It is a pMDI containing placebo as an inhalation aerosol. The placebo inhaler contains the same inactive excipients as the 3M Inhaler (without the active compounds).

Each inhaler contains 120 actuations.

3.4. Dose Adjustment/Modifications

No dose adjustments or modifications are allowed for this study.

4. General Statistical Considerations

In general, descriptive statistics will be presented by treatment group and by visit, as applicable. For continuous variables, summary statistics for the raw value and change from baseline at each time-point will include the number of subjects (n), arithmetic mean, standard deviation (SD), median, minimum and maximum.

Categorical variables will be summarized using subject counts and percentages. Percentages will be calculated using the total subjects per treatment unless otherwise specified.

Baseline demographic data are those collected at Screening. Baseline spirometry data for the primary endpoints are defined in Section 8. No baseline testing will be performed for this study.

The analysis set for assay sensitivity will be the Full Analysis Set and the analysis set for equivalence testing will be the Per Protocol Set. Analyses that are performed on the Full Analysis Set will use the planned treatment while analyses using the Per Protocol Set will use the actual treatment the subject received. See Section 4.4 for the Full Analysis Set and Per Protocol Set definitions.

The safety analysis will be conducted on the Safety Set using the actual treatment the subject received. See Section 4.4 for the Safety Set definition.

Listings will be presented by subject identifier and treatment group. In general, all listings will present all data for the Enrolled Set unless otherwise specified.

All statistical tests will be 2-sided and will be conducted at the 5% significance level, unless otherwise specified. P-values will be reported to 4 decimal places, with p-values less than 0.0001 reported as "<0.0001".

SAS® version 9.2 or higher will be used to perform all statistical analyses or procedures.

4.1. Sample Size

Approximately 1470 adult subjects (18 years of age or older) with asthma are proposed to be randomized to the 3 treatment groups in a 3:3:1 ratio (630 subjects per active treatment group and 210 in the placebo group).

4.1.1 Equivalence

The sample size calculations for equivalence are mainly driven by demonstrating equivalence for the change from baseline in trough FEV_1 (L) at the End-of-Treatment Visit (Week 6). Equivalence will be defined as the 90% CIs for the ratio (test/reference) falling within the (0.80, 1.25) target ratio. The sample size of 567 subjects in each active treatment group will provide approximately 87.1% power at the 5% significance level for the equivalence test of means using two 1-sided tests and assuming a true ratio of the means equal to 0.95, coefficient of variance (CV) of 1.00, and equivalence limits of the mean ratio of 0.80 and 1.25. Similarly, for AUC_{0-12} of the change from baseline in FEV_1at Day 1 endpoint, using an SD of xxx the sample size of 567 subjects in each active treatment group will provide 90.1% power at the 5% significance level for the equivalence test of means using two 1-sided tests and assuming a true ratio of the means equal to 0.95, CV of 0.95, and equivalence limits of the mean ratio of 0.80 and 1.25. The sample size will be based on the per-protocol set (PPS). Therefore, accounting for an approximate 10% dropout rate from the PPS, a sample size of 1470 subjects (630 subjects per active treatment group and 210 in the placebo group) is proposed.

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4.1.2 Superiority

For the change from baseline in trough FEV_1, the sample size of 630 in the active treatment group and 210 subjects in the placebo group will provide more than 99% power to reject the hypothesis of equal means at the 5% significance level using a 2-sided 2-sample equal-variance *t* test, assuming that the population mean difference xxx.

Similarly, for FEV_1AUC_{0-12}, the sample size of 630 in the active treatment group and 210 subjects in the placebo group will provide more than 99% power to reject the hypothesis of equal means at the 5% significance level using a 2-sided 2-sample equal-variance *t* test and using a population mean difference xxx.

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4.2. Randomization and Blinding

Subjects will be randomly assigned to receive budesonide/formoterol fumarate (80 µg/4.5 µg) via a 3M Inhaler, budesonide/formoterol fumarate (80 µg/4.5 µg) via a Symbicort Reference Inhaler, or placebo using a 3:3:1 allocation ratio. xxx. Each qualified subject who is randomly assigned to study treatment will receive 1 kit xxx. As each inhaler holds sufficient medication for 30 days of twice-daily dosing, 2 inhalers are required for the subject to have sufficient study medication for the 6-week treatment period. Each inhaler will be clearly labeled as Inhaler 1 and Inhaler 2.

This is a single-blind study. Subjects will not be informed of the study treatment to which they are randomly assigned. The appearance of the 3M Inhaler and the Symbicort Reference Inhaler are not identical so some subjects may be able to infer whether or not they have a Symbicort Reference Inhaler.

4.3. Treatment Periods

Placebo run-in period

The placebo run-in period is defined as the period between the date of the first dose of run-in placebo and the day prior to the date of the first dose of single-blind study drug, inclusive.

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Single-blind treatment period

For efficacy data, the single-blind treatment period is defined as the period between the date of first dose of single-blind study drug and the End-of-Treatment Visit (Week 6) date ± 2 day, inclusive.

Adverse events will be assessed beginning at enrollment (date of signed informed consent) and up to the End-of-Treatment Visit (Week 6). Even though the Investigator does not need to actively monitor subjects for AEs once the study has ended, SAEs occurring to a subject within 30 days after the last dose of study medication should be reported if the Investigator becomes aware of them.

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4.4. Analysis Sets

Data will be analyzed and summarized using the analysis sets defined below.

4.4.1. Screened Set

All subjects who signed the informed consent form (ICF). Screen failures are defined as subjects who never received placebo during the placebo run-in period and were not randomized in the study.

4.4.2. Enrolled Set

All subjects who took at least one dose of placebo run-in medication during the placebo run-in period. Run-in failures are defined as subjects who received the placebo study drug during the placebo run-in period but were not randomized in the study.

4.4.3. Randomized Set

All subjects randomly assigned to receive single-blind study treatment regardless of whether or not they received a dose of single-blind study medication. Mis-randomized subjects will be excluded.

4.4.4. Full Analysis Set

All randomized subjects who have taken at least one dose of single-blind study medication and have provided data for either the $FEV_1AUC_{0\text{-}12}$ endpoint measured on Day 1 or the endpoint for change from baseline in trough FEV_1 at the End-of-Treatment (Week 6), including the baseline FEV_1 value. All analyses using the FAS will group subjects according to randomized treatment. This analysis set will be used to assess the assay sensitivity of each active treatment (3M Inhaler and Symbicort Reference Inhaler) compared with placebo.

4.4.5. Per Protocol Set

All subjects in the Full Analysis Set who have not deviated from the protocol in such a way that could affect the outcome of the FEV_1 assessments for both primary endpoints.
Per definition, the PPS will only include subjects who received the single-blind study medication to which they were randomly assigned. This analysis set will be used to assess the therapeutic equivalence of 3M Inhaler compared with Symbicort Reference Inhaler.

4.4.6. Safety Set

All subjects who received any single-blind study medication. All analyses using the safety set will group subjects according to treatment actually received. All safety endpoints will be analyzed based on the Safety Set.

4.5. Spirometry Data Handling Conventions

4.5.1 Handling Spirometry Measurements with Unacceptable PFT Grade

FEV_1 measurements with a PFT grade of 'Unacceptable' after best test review (BTR) will be excluded from the ADaM dataset. However, all data will be retained in the SDTM dataset.

4.5.2 Handling Spirometry Data from Rescheduled Visits

Per protocol Section 6.1, subjects may present for repeat spirometry and reversibility testing 7 days (±1 day) after the Screening visit if they did not satisfy the FEV_1 acceptability criteria. Spirometry data resulting from the repeat visits will be included in summary tables, listings and statistical analyses. However, all data, including those from the original visits will be retained in the ADaM and SDTM datasets.

4.5.3 Handling Optional Spirometry Measurements

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4.5.4 Handling Missing Co-primary Endpoint Data

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5. Subject Disposition

5.1. Disposition

The number of subjects included in each analysis set will be presented by treatment group and overall. Three summary tables will be provided; one table for the Screened Set, a second table for the Enrolled Set and a third table for the Randomized Set.

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5.2. Protocol Deviations

Protocol deviations will be recorded within the xxx Clinical Trial Management System (CTMS) and will undergo a blinded review prior to database lock and unblinding. The 3M CSP-07-000034 Study Deviation Rules document contains potential protocol deviations, classified by CTMS subtype and whether the deviation is significant or not. xxx severity codes xxx will be assigned in order to identify significant deviations from the protocol that could affect inclusion/exclusion of subject data into the analysis sets or one of the sensitivity analyses.

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6. Demographics and Baseline Characteristics

6.1. Demographics

Demographic variables such as age, sex, race, ethnicity, height, weight, and body mass index (BMI) at baseline will be summarized. Continuous variables, such as age (years), body mass index, weight, height, asthma duration (years) and whether subject was on Short Acting β_2 Agonist (SABA) only at screening will be summarized using descriptive statistics for each treatment group. Categorical variables such as sex, ethnicity, and race will be summarized by reporting the number and percentage of subjects in each category for each treatment group. Summaries will be performed using the Full Analysis Set and Per Protocol Set.

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Demographic data will be listed using the Screened Set.

6.2. Baseline Disease Characteristics

Spirometry data at Screening visit will be summarized using the Full Analysis Set. These parameters will include FEV_1 (recorded as absolute volume in liters), both actual values and percent of predicted values; improvement and percent improvement in FEV_1 (reversibility); FVC actual values; FEV_1/FVC ratios. Baseline pre-dose spirometry measurements will also be summarized by time point, and treatment group using the Full Analysis Set.

Spirometry data during the Screening visit will be listed using the Full Analysis Set.

6.3. Medical History

6.3.1. General Medical History

Medical history of subjects will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting the study will be documented in the summary table footnotes. The number and percentage of subjects in each primary system organ class (SOC) and each preferred term (PT) will be summarized by treatment group using the Safety Set.

Each subject's medical history will be listed by SOC and PT using the Safety Set.

6.3.2. Disease-Specific History

No disease-specific history summary tables or listings will be presented.

6.4. Inclusion and Exclusion Criteria

Subjects (screen failures and run-in failures) who fail to fulfill all of the inclusion/exclusion

criteria will be listed for the Screened set.

7. Treatments and Medications

7.1. Concomitant Medications

Any prior and concomitant medication used during the study will be recorded and coded using WHODRUG. The WHODRUG version used for reporting the study will be documented in the summary table footnotes. Summaries of all medications by drug class (ATC Level 2 coding), preferred term and treatment group will be provided separately for prior medications and concomitant medications. xxxxx

All prior and concomitant medications will be listed for the Enrolled Set using verbatim and preferred terms.

7.2. Study Treatments

7.2.1. Treatment Compliance

Subject compliance will be assessed at the baseline visit (for the placebo run-in period inhaler) and at the End-of-Treatment Visit (Week 6) (for the single-blind study medication inhaler) using the dose counter on each inhaler. The diaries may also be used as a source for subject compliance, particularly when the study medications are not returned.

Subjects are expected to take two inhalations twice daily for a total of 4 doses daily. Subjects will be defined as compliant if at least 75% and no more than 125% of study medication doses are used. Subjects who are deemed noncompliant (ie, <75% and >125% of study medication doses are used) after the run-in period will be removed from the study.

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7.2.2. Extent of Exposure

Descriptive summary statistics including the number of subjects, mean, standard deviation, median, minimum, and maximum for the duration of study drug exposure (days) will be presented by treatment group. Single-blind study drug duration of exposure will be categorized and summarized as follows: 1 day, >1 to ≤7 days, >7 to ≤14 days, >14 to ≤21 days, >21 to ≤28 days, >28 to ≤35 days, >35 to ≤42days, >42 to ≤49 days and >49 days. Single-blind study drug exposure will be calculated as the number of days from first to last dose date of single-blind study drug.

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8. Efficacy Analysis

8.1. Primary Efficacy Endpoints

The co-primary endpoints for this study will be the AUC_{0-12} of the change from baseline in FEV_1 measured on Day 1 (Baseline visit) and change from baseline in trough FEV1 (L) at the End-of- Treatment Visit (Week 6). FEV_1AUC_{0-12} on Day 1 will be calculated from FEV_1 measurements collected 30 minutes prior to initial dose, at time point 0, and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dosing for the calculation of FEV_1AUC_{0-12}. The baseline for the FEV_1 AUC_{0-12} endpoint is the mean of the 2 pre-dose FEV_1 measures. In the unlikely event that either the 30 minute or 0 hour pre-dose FEV_1 value is missing, the mean will be set to the non-missing pre- dose measure for the Full Analysis set. However, for the Per Protocol set, such situation will result in a protocol deviation that removes the subject from the Per Protocol analysis. If both pre- dose values are missing then the baseline value will be missing.

FEV_1 AUC_{0-12} on Day 1 (Baseline visit) will be calculated as the area under the FEV_1 effect curve over 12 hours post dose on Day 1 (Baseline visit), estimated by the linear trapezoidal rule and corrected for the appropriate baseline FEV_1 value. The AUC formula by the trapezoidal rule is defined as:

$$FEV_1AUC_{0-12} = \sum_{i=1}^{i=n} \frac{c_i + c_{i-1}}{2} (t_i - t_{i-1})$$

here n = number of non-missing time points for that subject
i = sample number post-dose (i^{th} FEV_1 measurement on Day 1)
t_0 = clock time at dose administration
t_i = clock time at i
$c_0 = 0$, no change in FEV_1 from baseline at baseline time point
c_i = change in FEV_1 at t_i from baseline

xxxxx

The second co-primary endpoint, change from baseline in trough FEV_1 (L) at the End-of-Treatment Visit (Week 6) is based on two FEV_1 assessments performed 30 minutes apart on Day 42 (Week 6) or at the time of early discontinuation if subject terminates early from the study. The first spirometry assessment will be conducted at approximately the same time of day as the first pre-dose baseline spirometry assessment (ie, 30 minutes before initial dosing), and the second spirometry assessment will be performed at approximately 30 minutes later; the end-of-treatment FEV_1 value will be the average of the 2 assessments. If either of the 2 spirometry values is missing, then FEV_1 will be set to the non-missing value. The baseline FEV_1 is defined as the average of the 2 pre-dose FEV_1 values measured in the morning of the first day of treatment on Day 1. In the unlikely event that either the 30 minute or 0 hour pre-dose FEV_1 value is missing, the mean will be set to the non-missing pre-dose measure for the Full Analysis set. However, for the Per Protocol analysis, such situation will result in a protocol deviation that removes the subject from the Per Protocol Set.

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8.1.1. Primary Analysis

In order to show local equivalence, 3M Inhaler will be compared with the effect of Symbicort Reference Inhaler in delivering budesonide/formoterol fumarate (80 µg/4.5 µg) in a parallel group design; a placebo group will also be studied in order to show assay sensitivity for both primary endpoints. Assay sensitivity will be concluded if the p-value is less than 0.05 for the 3M Inhaler versus placebo and Symbicort Reference Inhaler versus placebo comparisons for both primary endpoints. It is anticipated that if the 2-sided 90% CI for the Least Squares (LS) mean ratios for both primary endpoints (3M Inhaler *vs.* Symbicort Reference Inhaler) are wholly contained within 80.00-125.00% limits, then this would be sufficient to show local equivalence [FDA, 2015].

The primary efficacy analysis will be performed to establish local equivalence of the 3M Inhaler vs. Symbicort Reference Inhaler. xxxxx

Equivalence Testing

Separate linear ANCOVA models will be fit for each primary endpoint. Treatment (3M Inhaler and Symbicort Reference Inhaler) will be included as a fixed effect. Baseline FEV_1 will be included as a continuous covariate.

Least Squares (LS) means will be derived for each treatment (3M Inhaler and Symbicort Reference Inhaler) for each primary endpoint. To establish equivalence, LS means from the ANCOVA models for each endpoint will be used to generate ratios (3M Inhaler/Symbicort Reference Inhaler). Fieller's theorem [Fieller E.,1954; Locke CS., 1984] will then be used to generate 2-sided CIs for the ratios for each endpoint. If the 2-sided 90% confidence intervals (CIs) for the ratios (3M Inhaler vs. Symbicort Reference Inhaler for each primary endpoint) are wholly contained within the interval 80.00-125.00% then we can conclude equivalence of 3M Inhaler to Symbicort Reference Inhaler.

Assay sensitivity

In order for the equivalence results to hold, assay sensitivity has to be established. For assay sensitivity the following comparisons need to be performed for each co-primary endpoint:

1) 3M Inhaler versus placebo
2) Symbicort Reference Inhaler versus placebo

A linear ANCOVA model will be fitted for each co-primary endpoint. All three treatments (3M Inhaler, Symbicort Reference Inhaler and placebo) will be included as fixed effects. Baseline FEV_1 will be included as a continuous covariate. LS means will be derived for each of the three treatments and LS mean differences will be calculated for 3M Inhaler versus placebo and Symbicort Reference Inhaler versus placebo for each primary endpoint.

Assay sensitivity will have been demonstrated if the p-values for all four comparisons are <0.05. No adjustment for multiplicity (i.e. potential loss of power due to making 4 comparisons) will be made because the primary endpoints are expected to be highly correlated.

8.1.2. Assumption Testing

The assumption of homogeneity of variances for the ANCOVA and Fieller's confidence intervals will be evaluated using a combination of several methods, including significance testing, Akaike information criterion (AIC) criteria and diagnostic statistics and plots. To evaluate homogeneity of variance using the AIC criteria, two models will be fitted: one model assuming equal variances and another model assuming unequal variances. If the model assuming equal variances has a significantly smaller AIC then this provides evidence towards potential homogeneity of variance among treatment groups. xxxxx

The same procedure for assessing homogeneity of variance will be applied to each of the sensitivity analyses of equivalence for the Per Protocol Set (see section 8.1.3). xxxxx

The normality assumption for the FEV_1 AUC_{0-12} endpoint and the change from baseline in trough FEV_1 (L) at the End-of-Treatment Visit (Week 6) endpoint data will be checked using residual plots. xxxxx

8.1.3. Sensitivity Analyses

As defined in Section 4.4.5, the Per Protocol Set will exclude subjects who have deviated from the protocol in such a way that could affect the outcome of both primary endpoints. However, the primary endpoints for this study are measured at different occasions. The FEV_1 AUC_{0-12} endpoint is measured on Day 1 (Baseline Visit) and the change from baseline in trough FEV_1 (L) at the End-of-Treatment Visit (Week 6) endpoint is measured at the End-of-Treatment Visit (Week 6). Therefore, it is entirely possible for a protocol deviation to affect one primary endpoint but not the other. xxxxx

Sensitivity analyses will be carried out for both assay sensitivity and equivalence, for both primary endpoints, using the Per Protocol Set as a reference. Subjects will be excluded based on significant adverse events, significant protocol deviations, compliance, missing data and procedural issues that are considered relevant to the outcome of the primary endpoint under consideration.

8.1.4. Covariate Analysis

A covariate analysis based on the PP Set for both the AUC_{0-12} of the change from baseline in FEV_1 measured on Day 1 endpoint and the change from baseline in trough FEV_1 (L) at the End-of-Treatment Visit (Week 6) endpoint assessing equivalence will be conducted to determine whether subjects who are on SABA only at Screening have a consistent treatment effect as all other subjects. ANCOVA models will be fit for each primary endpoint with treatment (3M Inhaler and Symbicort Reference Inhaler) included as a fixed effect, baseline FEV_1 and SABA only at Screening indicator as covariates, and SABA only at Screening indicator by treatment

interaction term. If the interaction term is significant, subgroup tables will be produced for SABA only subjects vs. all other subjects.

9. Safety Analysis

Safety will be assessed by all AEs noted during study participation (including exacerbation of preexisting conditions), changes in concomitant medication during study participation (including change in dose), and changes from baseline in vital signs, ECGs or laboratory results.

Adverse events will be assessed beginning at enrollment (date of signed informed consent) and up to the End-of-Treatment Visit (Week 6). Even though the Investigator does not need to actively monitor subjects for AEs once the study has ended, SAEs occurring to a subject within 30 days after the last dose of study medication should be reported if the Investigator becomes aware of them. A treatment-emergent AE is defined as any event not present before exposure to single-blind study medication or any event already present that worsens in either intensity or frequency after exposure to study medication.

All analyses of safety will be conducted using the Safety Set.

9.1. Adverse Events

A subject with multiple adverse events within a primary SOC or preferred term is only counted once towards the total for that SOC and/or preferred term. For the AE severity and relationship summaries, if a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity or relationship will be presented. If a subject reported more than one adverse event within the same primary system organ class, then the subject will be counted only once with the greatest severity or relationship at the system organ class level. For table summaries, if severity is missing then 'severe' is assumed. If relationship is missing, relationship to study drug is assumed to be 'related'.

The number and percentage of subjects with treatment emergent adverse events as well as the number of events will be summarized in the following ways:

- by primary system organ class, preferred term and treatment group
- by primary system organ class, preferred term, maximum severity and treatment group
- by primary system organ class, preferred term, relationship to study drug and treatment group

The most common adverse events reported will be presented by preferred term in descending frequency starting from the most common event.

The number and proportion of subjects as well as the number of events with the following types of events will be summarized by primary system organ class, preferred term and treatment:

- Adverse events leading to treatment discontinuation
- Serious Adverse Events (SAEs)
- Deaths

All adverse events, regardless of study period, will be included in a listing using the Screened Set. In addition the following select adverse events will be displayed in separate listings:

- Deaths
- Serious adverse events
- Adverse events leading to dose interruption
- Adverse events leading to treatment discontinuation
- Adverse events requiring concomitant or additional treatment

The above listings will use the Enrolled Set except for serious adverse events which will be listed for the Screened Set.

9.2. Clinical Laboratory Evaluations

Any data collected from the laboratory testing must be available in the source documents but will not be added to the analysis database. An abnormal laboratory value at the screening visit will be captured in the medical history. An abnormal laboratory value at the End-of-Treatment Visit (Week 6) that has worsened since the screening visit will be captured as an AE.

9.3. Physical Examination and Vital Signs

All data collected from the physical examinations and vital sign assessments must be available in the source documents but will not be added to the analysis database. An abnormal vital sign value or physical examination finding at the screening visit will be captured in the medical history. An abnormal vital sign value or physical examination finding at the End-of-Treatment Visit (Week 6) that has worsened since the screening visit will be captured as an AE.

9.4. Electrocardiogram

No ECG summary tables or listings will be presented. Data collected from the electrocardiogram assessments must be available in the source documents but will not be added to the analysis database.

9.5. Pregnancy

For females of childbearing potential only, a urine pregnancy test must be conducted at the screening and baseline visits, and a serum pregnancy test must be obtained at the screening and end-of-treatment visits. Both urine and serum pregnancy results will be included in the data listing.

10. Interim Analysis

There is no interim analysis planned for this study.

11. Blinded Sample Size Re-estimation

A blinded sample size re-estimation may be performed after 30% of the subjects are enrolled to check for the sample size assumptions and, if necessary, increase the sample size. However, if a sample size re-estimation was to be performed, details would be prespecified in a protocol amendment prior to any statistical analysis of the data.

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13. Appendices

13.1. Schedule of Study Procedures

This table provides an overview of the protocol visits and procedures in the Schedule of Events Section of the study protocol.

Procedure	Screening Visit[1]	Baseline Visit	Telephone Contacts		End of Treatment
Visit Day/Window	-21 days to -14 days	Day 1 (12-hour visit)	Day 14 ±2 days	Day 28[2] ±2 days	Day 42 ±2 days
Informed consent	X				
Medical history	X				
Demographics	X				
Electrocardiogram	X				
Safety laboratory assessment (obtained locally)	X				X
Physical examination (with height [screening only] and weight)	X				X
Pregnancy test[3]	X	X			X
Vital sign (blood pressure and heart rate) assessments	X	X			X
Spirometry assessments[4]	X	X			X
Inclusion/exclusion criteria review	X	X			
Randomization using IWRS		X			
Inhaler training	X	X			
Dispense placebo run-in period inhaler	X				
Dispense rescue therapy inhaler[5]	X	X			
Dispense study medication		X			
Concomitant medications	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X
Training and dispensing of handheld device to collect xxx diary information	X				
Study medication compliance and diary monitoring (retraining, as needed)		X	X	X	
Diary collection					X

[1] Following the screening visit, there will be 14- to 21-day run-in period. If needed, subjects can also rescreen. See Section 3.2 for additional details on the run-in period and on rescreening.

[2] At the Day 28 (Week 4) visit, subjects will be instructed to switch to the second inhaler beginning with the evening dose on the day of the telephone visit. Subjects will be reminded not to take study medication within 12 hours (±2 hours) of the start time of their end-of-treatment visit.

[3] For females of childbearing potential only, a urine pregnancy test must be conducted at the screening and baseline visits, and a serum pregnancy test must be obtained at the screening and end-of-treatment visits. See Appendix 2 for a definition of childbearing potential.

[4] See Section 6.1 for details on each spirometry assessment.

[5] Ensure that the subject has enough rescue therapy (see Section 5.2.2) for the remainder of the study.