Statistical Analysis Plan

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

Statistical Analysis Plan Approval Date: 11 April 2018

Statistical Analysis Plan	
Study code	ACT-2015-075-0AA
Version	Final
Date	Apr 11, 2018

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 Statistician

<<*Name*>> Date

Sponsor Representative

<<*Name*>> Date

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
BDRM	Blinded Data Review Meeting
BDS	Budesonide
BMI	Body Mass Index
CI	Confidence interval
CV	Coefficient of variation
D1PPS	Day 1 Per-protocol Set
D42PPS	Day 42 Per-protocol Set
eCRF	Electronic case report form
ENS	Enrolled Set
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEF_{25-75}	Forced expiratory flow 25%-75%
FEV_1	Forced expiratory volume in one second
FEV_1 AUC_{0-12}	Area under the FEV_1 curve calculated from time 0 (zero) to 12 hours
FFD	Formoterol Fumarate Dihydrate
FVC	Forced Vital Capacity
ICS	Inhaled corticosteroids
IWRS	Interactive Web Response System
LABA	Long-acting β2-adrenergic agonist
mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NAEPP 3	National Asthma Education and Prevention Program Expert Panel Report 3
NDA	New Drug Application
NHANES	National Health and Nutrition Examination Survey
LS mean	Least-squares mean
PEFR	Peak expiratory flow rate
PID	Patient identification
pMDI	Pressurized metered dose inhaler
PPS	Per-protocol Set
PT	Preferred term
RiN	Run-in Set
RLD	Reference Listed Drug
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event

TMF	Trial Master File
US	United States

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol "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", version 3.0, amendment 1.0, dated February 27, 2017.

Watson Laboratories, Inc. is developing a new generic formulation of budesonide 80 mcg/formoterol fumarate dihydrate 4.5 mcg inhalation aerosol for which demonstration of bioequivalence to the reference product (i.e., Symbicort®) is required. This study is designed to evaluate the bioequivalence between the administered test and reference products in accordance with the recommendations outlined in the US Food and Drug Administration (FDA) Draft Guidance on Budesonide; Formoterol fumarate dihydrate (June 2015).

2. OBJECTIVES

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 pressurized metered dose inhaler (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 reference products should both be statistically superior to placebo ($p<0.05$) with regard to the study primary endpoints.

3. STUDY OVERVIEW

3.1 Study Design

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 [redacted] 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, non-lactating 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 forced expiratory volume in 1 second (FEV_1) of ≥45% and ≤85% of the predicted normal value using the equations derived from the National Health and Nutrition Examination Survey (NHANES) III dataset for adults. All lung function tests will be conducted in accordance with current American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations.

Patients must demonstrate ≥15% reversibility of FEV_1 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 ± 10 minutes) are permitted at Visit 1. If the patient achieves <15%, but ≥10% reversibility at Visit 1, the site may instruct the patient to hold long-acting β2-adrenergic agonist (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 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, unless approved by the Sponsor and Medical Monitor) to wash out any pre-study corticosteroids or long-acting bronchodilators and to establish FEV_1 baseline values.

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

Patients must have placebo inhaler compliance of at least 70% (rounded to whole number) of study drug doses in the Run-in Period to proceed into the randomized Treatment Period. Compliance will be based on patient eDiary documentation of doses taken from the eCOA Visit 1 date (which may differ from the eCRF Visit 1 date due to rescreening or other delays in the start of placebo administration) until the Visit 2 date.

Randomized Treatment Period

Those continuing to meet entry criteria will enter a 6-week Treatment Period (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 [redacted] for Watson Laboratories Inc.) (Test Drug)
- Reference product (RLD): Symbicort® (manufactured by AstraZeneca) (Reference Drug)

- Placebo: To match generic BDS 80/FFD 4.5 inhalation aerosol (manufactured by [redacted] for Watson Laboratories Inc.) (Placebo)

On the first day of treatment at Visit 2, FEV_1 will be determined at approximately 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 + 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, FEV_1 will be determined at 60, 30, and 5 minutes pre-dose, the average of which constitutes the pre-dose (0) value. If only one acceptable session is available, it will be used as the pre-dose (0) value.

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.

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

A detailed Schedule of Procedures is provided in Appendix 12.1.

3.2 Sample Size

Patients will be enrolled in a [redacted] ratio of test:reference:placebo. Approximately 1130 patients will be randomized[redacted]

[redacted]

Table 1 summarizes the sample size calculation.

Table 1 Sample Size Calculation

Popula- [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[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:

1. [redacted]
2. [redacted]
3. [redacted],

4. [redacted]
5. [redacted]
6. [redacted]

[redacted].

Estimates of sample size were calculated under the additional following assumptions for comparisons with placebo:

1. [redacted]
2. [redacted]
3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.3 Randomization and Unblinding Procedures

3.3.1 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 subject 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.

3.3.2 Randomization Scheme

Subjects will be randomly assigned to treatment on a [redacted] basis to generic BDS 80/FFD 4.5 inhalation aerosol manufactured by [redacted] for Watson Laboratories Inc. (Test Drug), Symbicort® (Reference drug), or Placebo, respectively.

3.3.3 Allocation/Randomization of Subjects 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.

4. STUDY ENDPOINTS/OUTCOMES

This study's co-primary efficacy endpoints are:

- Baseline-adjusted area under the serial FEV_1-time curve calculated from time 0 (zero) to 12 hours on the first day of the Treatment Period (Visit 2, Day 1).
- Baseline-adjusted, pre-dose FEV_1 collected in the morning before dosing on the last day of treatment (Visit 4, Day 42). The FEV_1 Baseline is defined as the average of the pre-dose FEV_1 values obtained on Day 1. The Visit 4 FEV1 value will be measured as the mean of acceptable values collected at the visit or a single measurement if only one acceptable (per ATS criteria) spirometry session is obtained.

5. HYPOTHESES TESTING

Hypothesis of Equivalence

A two-sided, 90% confidence interval on the test/reference ratio for each of the study's co-primary endpoints will be constructed using an Analysis of Covariance (ANCOVA) model of the Test and Reference results with treatment and study site as fixed effects and baseline FEV_1 as covariate, further applying Fieller's method.

Clinical endpoint bioequivalence will be established if the 90% confidence intervals for the ratio of test/reference means, for both endpoints, are contained within the interval [80.00%, 125.00%] for the Per-protocol Set.

Hypothesis of Superiority

In order to demonstrate adequate sensitivity, both test and reference treatments will be compared with placebo with respect to the primary endpoints using an ANCOVA model with treatment and study site as fixed effects and baseline FEV_1 as covariate. Both treatments must be statistically superior to placebo for the Modified Intent-to-Treat Set in order to validate the assessment of clinical endpoint bioequivalence for the test/reference ratios for the co-primary endpoints.

6. ANALYSIS SUBSETS

6.1 Enrolled Set (ENS)

The Enrolled Set (ENS) will consist of all subjects who provided informed consent/assent.

6.2 Run-in Set (RiN)

All patients who enter the Run-in Period.

6.3 Randomized Set

The randomized set will consist of all subjects who were randomized.

6.4 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will consist of all randomized subjects who received at least 1 dose of randomized study drug during the Treatment Period. Subjects will be classified by actual treatment received. The SAF will be the primary population for the safety analysis.

6.5 Modified Intent-to-Treat (mITT) Set

The Modified Intent-to-Treat (mITT) set will consist of all randomized subjects who received at least 1 dose of randomized study drug during the Treatment Period. [redacted]. Duplicate subjects (those who enrolled at more than one study site), will be excluded from the mITT if their enrollment overlaps. [redacted]. Subjects will be classified by the treatment to which they were randomized. This population will be considered as definitive for testing superiority.

6.6 Per-protocol Set (PPS)

[redacted]

[redacted]

7. STATISTICAL METHODS OF ANALYSIS

7.1 General Principles

The statistical analyses will be performed by [redacted] with approval of the Sponsor, using SAS Version 9.3 (or higher). All tables, figures and listings will be produced in landscape format.

In general, all data will be listed by subject and visit/time point where appropriate. The summary tables will be stratified by, or have columns corresponding to, treatment groups.

The total number of subjects in the treatment group (N) under the stated analysis set will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. Number of subjects with missing values will also be displayed, but only if non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data. The standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be displayed. The count [n] indicates the actual number of subjects in a particular category, which should always be less than or equal to the total number of subjects in the respective study group with known (non-missing) category [M]. Percentage will be obtained by: % = n/M*100. Unless otherwise specified, all percentages will be expressed to one decimal place.

All statistical tests will be two-sided at a significance level of $\alpha = 0.05$, unless otherwise indicated. No adjustment will be made for multiplicity.

Baseline will be defined as the last assessment, scheduled or not, prior to the first dose of the randomized study drug, unless otherwise specified.

In by-visit summaries, only data collected on scheduled timepoints will be summarized. Data from unscheduled assessments will be included in listings and may be used in determination of baseline if applicable.

Relative days will be calculated relative to date of first dose of randomized study medication. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days).

For assessment on or after the day of first dose of the randomized study drug:

Relative Day = Date of Assessment – Date of First Dose of Randomized Study Drug+1.

For assessment before the day of first dose of the randomized study drug:

Relative Day = Date of Assessment – Date of First Dose of Randomized Study Drug.

All dates will be displayed in DD/MMM/YYYY format.

7.2 Subject Disposition

This analysis will be based on the ENS. The number of subjects enrolled in the study, randomized to treatment, included in the SAF, mITT, [redacted] PPS, prematurely discontinued from the study after randomization (along with the reasons for discontinuation) will be presented. The same analysis will be repeated by study site.

An overall summary of the number of subjects in each population by site will be created.

All disposition information will be listed. Additionally, a listing of subjects who discontinued from the study prematurely will be created, including date of discontinuation and primary reason. Also a listing of enrollment details will provide the date of informed consent/assent and inclusion/exclusion criteria not met, if any.

7.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will include:

- age
- sex
- race
- ethnicity

- baseline height, weight and body mass index (BMI)
- time since asthma diagnosis (years)
- if subject was hospitalized for asthma exacerbation (yes or no)
- if subject has any other lung disease (yes or no).

Descriptive statistics will be presented for continuous variables. Frequency counts and percentage will be presented for categorical variables. Height will be reported in centimeters, weight in kilograms and BMI in kg/m^2.

Age will be derived from Informed Consent/Assent Date and Date of Birth as the number of whole years between those two dates.

Demographic and baseline characteristics will be evaluated for comparability across treatment groups in the following manner. Continuous variables will be analyzed with an analysis of variance with factors of treatment and investigational site. Overall p-value for the global null hypothesis of all groups being equal will be displayed. Categorical variables will be analyzed with a Cochran-Mantel-Haenszel general association test, stratified by investigational site.

These analyses will be performed for the SAF, mITT, [redacted] PPS.

All demographic parameters and baseline characteristics will be presented in the by-subject listings.

7.4 Medical history

Medical history will be summarized by MedDRA (version 20.0) System Organ Class and Preferred Term. This summary will be performed for the SAF. All medical history information will be listed.

7.5 Protocol Deviations

Protocol deviations will be derived algorithmically as well as reported by sites. Each protocol deviation will be classified as minor or major. [redacted]

Specific deviation and their severity are defined in the separate Protocol Deviations List document.

All major protocol deviations will be summarized by deviation category and treatment group. This analysis will be performed for the Randomized set.

7.6 Lung function testing

The results of the spirometry measurements (including reversibility testing) at Visit 1 Screening will be listed for each subject including the FEV_1, FVC, FEV_1 to FVC ratio, FEF_{25-75} (absolute values and percentage of predicted values rounded to whole numbers). For the reversibility testing, both the absolute measurements and percentage change after inhaled albuterol (or equivalent) will be presented.

Spirometry data from the vendor include quality assessment that ranges from 'A' to 'F'. [redacted]

The results will be summarized by treatment and parameter for the mITT set, the [redacted] PPS. For subjects who repeated reversibility testing at a repeat screening visit, only the repeat value will be used for analysis (provided it meets acceptability criteria above).

7.7 Efficacy Analyses

7.7.1 Analysis of Equivalence and Superiority

7.7.1.1 Calculation of the Primary Endpoints

Acceptability criteria. Spirometry data from the vendor include quality assessment that ranges from 'A' to 'F'. [redacted]

FEV_1 baseline. The FEV_1 baseline will be defined as the average of the pre-dose FEV_1 values obtained at Visit 2 Day 1. If some of these measurements are missing, the average will be calculated using the available measurements, however, a minimum of two pre-dose FEV_1 values is required; subjects who have only one or no pre-dose FEV_1 measurements on Day 1 will have their FEV_1 baseline missing, and this the subject will be excluded from analysis.

Calculation of FEV_1 AUC_{0-12}. The endpoint of Baseline-adjusted FEV_1 AUC_{0-12} on Day 1 will be calculated as follows:

1. Each FEV_1 assessment on Day 1 will be baseline-adjusted by subtracting the FEV_1 baseline value defined above.

2. FEV_1 AUC_{0-12} will be calculated from the baseline-adjusted values using the linear trapezoidal method. The calculation will assume that at time of dosing (time 0) the baseline-adjusted FEV_1 is also 0. The calculation will proceed over all available post-dose FEV_1 assessments on Day 1 (including unscheduled timepoints, if any) using actual elapsed time from dosing.
3. FEV_1 AUC_{0-12} will be considered non-computable in a subject if one of the following occurs in that subject:

[redacted]

Calculation of Baseline-adjusted pre-dose FEV_1 at end of treatment.

The endpoint of Baseline-adjusted pre-dose FEV_1 at end of treatment will be calculated as

[FEV_1 at end of treatment] – [Baseline FEV_1]

where FEV_1 at end of treatment will be defined as the single or average (if multiple available) pre-dose assessment(s) at Visit 4 Day 42. At least one acceptable pre-dose assessment at Visit 4 Day 42 is required to calculate the change from baseline. If more than one acceptable pre-dose assessment is available, the average will be used in the calculation.

If a subject has no pre-dose assessment at Visit 4, Day 42, in the mITT analysis Average FEV_1 at end of treatment will be imputed (following LOCF rule) as the average of available pre-dose assessments on the last post-baseline day when at least two pre-dose FEV_1 assessment are available (e.g. the Early Termination visit). [redacted]. In the PPS analysis, however, the endpoint will not be imputed and the subject will be thus excluded from analysis, unless the subject missed Visit 4 Day 42 because he/she discontinued from the study due to lack of efficacy. In the latter case the endpoint will be imputed in the same way as for mITT analysis even in the PPS analysis.

7.7.1.2 Site pooling

To eliminate potential effect of random fluctuations at small sites on the primary endpoints small sites will be pooled. The data of a study site will be pooled if it meets either of the following conditions:

- [redacted]
- [redacted].

The sites with the lowest number of patients that does not meet the above requirements will be pooled with the next largest site within the same geographical region until a pooled site meets the above two requirements. Pooled sites will obtain a new identification number that will be used in analyses of equivalence and superiority.

[redacted].

7.7.1.3 Analysis of clinical equivalence of test and reference treatments

To show the clinical equivalence, the following steps will be taken separately for each co-primary endpoint:

1. An ANCOVA model will be fit on the subjects from the Test and Reference groups only, with the endpoint as outcome and treatment, study site and treatment-by-site interaction as fixed effects and FEV_1 baseline value as covariate. If the treatment-by-site interaction factor is not significant at the 0.05 level, the model will be rerun without the interaction term. Treatment LS means and standard errors will be estimated from this model. Then Fieller's formula will be applied to calculate the 90% confidence interval for the Test/Reference LS mean ratio; covariance between treatment means will be assumed to be 0. See appendix 12.2 for a complete description of Fieller's formula.
2. Clinical equivalence will be declared if the 90% confidence interval for the test/reference LS mean ratio for both endpoints is entirely contained within the interval from 80% to 125%.

Analysis of clinical equivalence will be performed on [redacted] PPS [redacted] .

7.7.1.4 Analysis of superiority to placebo

The analysis of superiority will be performed separately for each of the 2 co-primary endpoints and separately for the Test treatment versus the Placebo and for the Reference treatment versus the Placebo. Each of these analyses will be performed as follows:

1. ANCOVA models will be fit on the subjects from the two treatment groups only (Test and Placebo for the analysis of superiority of Test to Placebo and Reference and Placebo for the analysis of superiority of Reference to Placebo), with the endpoint as outcome and treatment, study site and treatment-by-site interaction as fixed effects and FEV_1 baseline value as covariate. If the treatment-by-center interaction factor is not significant at the 0.05 level, the model will be rerun without the interaction term. Treatment LS mean and LS mean difference (Test or Reference - Placebo), its 95% confidence intervals and the p-value for the hypothesis of no treatment effect will be obtained from the model.
2. Superiority will be declared if the Test and Reference LS means are each greater than the Placebo LS mean and the respective p-values are < 0.05.

Analysis of superiority for both endpoints will be performed on the mITT set.

7.7.2 Analyses of FEV_1

Spirometry data from the vendor include quality assessment that ranges from 'A' to 'F' [redacted]

All post-baseline FEV_1 assessments (both absolute and baseline-adjusted values) will be summarized descriptively by timepoint and treatment group. All FEV_1 assessments (both absolute and baseline-adjusted values) will also be listed. These analyses will be performed for the mITT set, [redacted] PPS.

Mean FEV_1 (both for absolute and baseline-adjusted values) on Day 1 will be plotted graphically by treatment group, for the mITT set and [redacted] PPS.

FEV_1 AUC_{0-12} on Day 1 and FEV1 at end of treatment (both absolute and baseline-adjusted) will be summarized descriptively by treatment group and listed, for the mITT set and the PPS appropriate for each endpoint.

7.8 Safety Analyses

All safety analyses will be performed on the SAF.

7.8.1 Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA version 20.0) AE coding system for purposes of summarization.

Only Treatment Emergent Adverse Events (TEAE) starting will be used for the summary analysis. An AE will be considered as treatment-emergent if the time of onset is on or after the time of the first placebo administration in the study Run-in period. AEs with unknown start dates will be counted as treatment-emergent unless the AE resolution date is prior to the placebo start date. If the start date is partially missing, the AE will be considered treatment-emergent, unless the month and year (when available) rule out the possibility that the event occurred post dosing.

All AEs will be assigned to study periods for the purposes of the tabulations:

Run-in Period: All TEAEs with onset at the time on or after the first dose of placebo study drug during the Run-in Period until the time of the first dose of randomized study drug.

Treatment Period: All TEAEs with onset at the time of or after the first dose of randomized study drug during the Treatment Period.

For the purposes of assigning TEAEs to study periods partial onset dates will be imputed as the latest possible date compatible with the known partial information; thus in case of ambiguity TEAEs will be assigned to Treatment period.

A TEAE is defined as treatment-related if it is recorded as related, probably related or possibly related to the study medication on the eCRF. In case the relatedness was not assessed, the most conservative result (related) will be chosen for the analysis.

In summaries of TEAEs a subject experiencing the same AE multiple times will only be counted once for that preferred term. Similarly, if a subject experiences multiple AEs within

the same system organ class that subject will be counted only once in that system organ class. When summarizing AEs by severity, only the most severe occurrence within the preferred term or system organ class will be used. Similarly, when summarizing AEs by relationship to study drug, only the most related occurrence within the preferred term or system organ class will be selected for displays in summary tables.

An overall summary will include, by study period and by treatment group and overall, the number and percentage of subjects reporting at least 1 TEAE in the following categories:

- Any TEAE
- Treatment-related TEAE
- Serious TEAE
- TEAE leading to discontinuation of the study medication
- TEAE leading to death.

The following TEAE frequency tables will be prepared summarizing the overall number of TEAEs, the number and percentage of subjects reporting at least one TEAE by MedDRA System Organ Class (SOC) and preferred term (PT), by treatment group and by study period:

- All TEAEs
- Serious TEAEs
- Treatment-related TEAEs
- AEs leading to discontinuation of the study medication
- TEAEs by Severity
- TEAEs by Relationship to Study Medication.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim, preferred term, system organ class, start date, stop date, intensity, outcome, action taken and causal relationship to the study drug. The adverse event onset will also be shown relative (in number of days) to the date of first administration of the study medication.

In addition the adverse event duration (if AE Stop Date is available) will be evaluated as below and presented (in number of days).

AE Duration = AE Stop Date – AE Start Date + 1

7.8.2 Laboratory tests

Laboratory safety assessment (i.e., clinical chemistry and hematology) 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.

Pregnancy test results and results of the drug and alcohol screen will be listed.

7.8.3 Vital signs

Vital signs include blood pressure, pulse, respiratory rate, and body temperature and will be measured at each visit, as well as at any unscheduled visit. Overall interpretation will also be recorded as Normal, Abnormal not clinically significant or Abnormal clinically significant.

Vital signs will be summarized descriptively by scheduled visit and treatment group. For visits in the Treatment period the change from baseline will also be summarized.

Overall interpretation of vital signs will be summarized categorically by visit.

All vital signs will be listed.

7.8.4 12-Lead ECG

ECG will be performed at Visit 1 Screening and Visit 4 Day 42 or early termination. The values of PR interval, QRS duration, RR interval, QT interval and QTcB interval will be collected, as available. Overall interpretation will be recorded as Normal, Abnormal not clinically significant or Abnormal clinically significant.

Number and percentage of subjects with each level of interpretation will also be summarized by visit and treatment.

All ECG findings will be listed.

7.8.5 Physical Examination

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

7.8.6 Peak Expiratory Flow Rate

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

PEFR values will be summarized graphically. A line plot will be created with X axis showing study day (-14 to 42) and Y axis showing mean PEFR. A separate line will be plotted for each treatment group.

7.8.7 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]
- [redacted]
- [redacted]
- [redacted]

Asthma symptom score will be summarized graphically. A line plot will be created with X axis showing study day (-14 to 42) and Y axis showing mean symptom score. A separate line will be plotted for each treatment group.

7.8.8 Exposure to Product

The subjects will be instructed to use the diary to document all doses taken.

[redacted]:

- [redacted]

[redacted]

- Planned number of doses is determined as follows:

  [redacted]

  - Treatment period:

    - [redacted]

    - [redacted]

Note that in the calculation of the planned number of doses for the run-in period the date of Visit 1 is taken from the [redacted] (spirometry vendor) data. It may differ from the CRF data if subjects return for repeat spirometry assessments. In such cases the [redacted] data will record the repeat visit as Visit 1. The intent is to take the date of the repeat spirometry visit, if one occurred, and the date of the original screening visit, if no repeat occurred.

All doses in the diary recorded on or after the date of Visit 2 and dosing time as reported in the spirometry data will be considered as belonging to the Treatment period. All doses in the diary prior to that date and time will be considered as belonging to the Run-in period.

Compliance will be rounded to whole percentages. During the Run-in period, subjects will be considered compliant if they take at least [redacted]. For the treatment period, subjects will be considered compliant if they take at least 75% and not more

than 125% of doses. The compliance will be analyzed using the descriptive statistics by study period and treatment group. The proportion of compliant vs. non-compliant subjects will be tabulated for each study period and treatment group.

Duration of exposure will be calculated by study period as [Date of last use of study medication in the period] – [Date of first use of study medication in the period] + 1. Duration of exposure will be summarized descriptively by study period and treatment group.

Compliance and duration of exposure will also be listed.

These analyses will be performed for the SAF.

Diary compliance will be determined only for the purposes of identification of protocol deviations. Diary compliance will be determined based on the compliance report from BMS similar to study drug compliance. In the Run-in period: "Run-In: Actual Number of Questionnaire Completions" / "Run-In: Expected Number of Questionnaire Completions". In the Treatment period: ("Treatment V2-V3: Actual Number of Questionnaire Completions" + "Treatment V3-V4: Actual Number of Questionnaire Completions") / ("Treatment V2-V3: Expected Number of Questionnaire Completions" + "Treatment V3-V4: Expected Number of Questionnaire Completions") * 100%.

7.8.9 Rescue medication use

Number of rescue medication uses in Run-in and Treatment periods will be counted in the diary, using the answers from "AM Questionnaire" ("If you had difficulty sleeping during the night because of asthma symptoms, did you need to take albuterol/salbutamol (your rescue medication)?") "PM Questionnaire" ("Did you need to take albuterol/salbutamol (your rescue medication)?") and "Missed Recoding Questionnaire" ("Did you take your rescue medication yesterday morning (12:00am-11:59am)?" and "Did you take your rescue medication yesterday afternoon or evening (12:00pm-11:59pm)?"). This number will be summarized descriptively by study period and treatment group. It will also be listed.

7.8.10 Prior and Concomitant Medication

Prior and concomitant medication will be coded according to the World Health Organization – Drug Reference List and the Anatomical Therapeutic Chemical 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.

All previous and concomitant medication will be listed by subject. Concomitant medications will be summarized by treatment group, ATC class (highest level available) and preferred name. This analysis will be done for the SAF.

8. INTERIM ANALYSIS

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

[redacted]

9. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

The following changes from the protocol specified analysis have been made:

10. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

See separate document with the table, figure and listing shells.

11. LITERATURE CITATIONS / REFERENCES

1. Study protocol: "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", version 3.0, amendment 1.0, dated February 27, 2017
2. Draft Guidance on Budesonide; Formoterol fumarate dihydrate, Jun 2015.

12. APPENDICES

12.1 Study visit Schedule

Procedure/Assessment	Screening	Run-in Period[1]	Treatment Period				
	Visit 1 Day -14	Days -13 to -1[2]	Visit 2 Day 1 +7 days*	Days 2-20	Visit 3 Day 21±7 days*	Days 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[14]		X[14]		
Dispense study drug	X[15]		X		X		
Resupply rescue medication[13]					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, FEV_1: 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 ≥45% and ≤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 ≥45% and ≤85% of the predicted value.

9. Patients must demonstrate ≥15% reversibility of FEV1 within 30 minutes following 360 mcg of albuterol/400 mcg salbutamol inhalation pMDI. If the patient achieves <15%, but ≥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. Patients will also inhale from the [redacted] training device to simulate the resistance of the pMDI. 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.

[redacted]