

Statistical Analysis Plan with Amendment 01

A 12-Week, Open-Label Study to Evaluate the Relationship Between Use of Albuterol eMDPI, an Inhaled Short-Acting Beta Agonist “Rescue” Agent with an eModule, and Exacerbations in Patients (40 Years of Age or Older) with Chronic Obstructive Pulmonary Disease

Study Number ABS-COPD-30065

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: ABS-COPD-30065

Study Title: A 12-Week, Open-Label Study to Evaluate the Relationship Between Use of Albuterol eMDPI, an Inhaled Short-Acting Beta Agonist “Rescue” Agent with an eModule, and Exacerbations in Patients (40 Years of Age or Older) with Chronic Obstructive Pulmonary Disease

Statistical Analysis Plan for:

- Interim Analysis
- Final Analysis
- Integrated Summary of Efficacy
- Integrated Summary of Safety

Amendment: 01

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AMENDMENT HISTORY

The Statistical Analysis Plan for study ABS-COPD-30065 (study protocol with amendment 03 dated 26 June 2017) has been amended and reissued as follows:

Amendment number	Date	Author(s)	Summary of Changes	Reason for Amendment
01	27 April 2018	[REDACTED]	Sections 3, 5.2, 5.10, 7, and 10 updated to indicate that all endpoint and safety analyses will use the ITT analysis set.	Decision by study team
			Section 4.4 updated to indicate whichever comes first.	Clarification
			Section 7.1.1 updated to reflect that the category with the highest number of inhalations will be reported if there is a tie in the most frequent usage.	Clarification
			Section 7.5.2 updated with modified analyses.	For this exploratory study, analyses methods were updated in the spirit of the protocol to better address study objectives and to align with the ancillary analytics report.
			Section 7.5.2.4 updated.	Clarification
			Section 7.5.3 updated to clarify that the analyses will be done by the data analytics group.	Clarification
			Section 10.4 updated to clarify the definition of treatment emergent.	Clarification

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ABS	albuterol sulfate
BMI	body mass index
CE-COPD	clinical exacerbation of COPD
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
D _{emdpi}	eMDPI time on study
eCRF	electronic case report form
EDC	electronic data capture
eMDPI	multidose dry powder inhaler with an eModule
FEV ₁	forced expiratory volume in 1 second
GCP	Good Clinical Practice
ICF	informed consent form
ICS	inhaled corticosteroid
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	Intent-to-Treat
LABA	long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
MDI	metered dose inhaler
MDPI	multidose dry powder inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MIF	maximal inhalational flow
mITT	Modified Intent-to-Treat
PP	Per-Protocol
R&D	Research and Development
SABA	short-acting beta ₂ agonist
SAMA	short-acting muscarinic antagonist
SCS	systemic corticosteroid
SD	standard deviation

Abbreviation	Term
SDI	sleep disruption index
SE	standard error
TDS	total daily steps
SOC	system organ class
SOP	standard operating procedure
WHO	World Health Organization

INTRODUCTION

This Statistical Analysis Plan describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. Study ABS-COPD-30065 (A 12-Week, Open-Label Study to Evaluate the Relationship Between Use of Albuterol eMDPI, an Inhaled Short-Acting Beta Agonist “Rescue” Agent with an eModule, and Exacerbations in Patients (40 Years of Age or Older) with Chronic Obstructive Pulmonary Disease), and was written in accordance with standard operating procedure (SOP) GBP_RD_702 (Statistical Analysis Plan).

The reader of this Statistical Analysis Plan is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study. The Statistical Analysis Plan is intended to be in agreement with the protocol. However, the Statistical Analysis Plan may contain more details regarding these particular points of interest, or other types of analyses (eg, other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this document, the Statistical Analysis Plan prevails; the differences will be explained in the clinical study report (CSR) or in this document.

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Objectives and Endpoints

The objectives of this study are to explore the pattern and amount of albuterol use (as captured in the albuterol sulfate (ABS) multidose dry powder inhaler with an eModule (eMDPI), alone or in combination with other study data, preceding a moderate or severe CE-COPD (as diagnosed by the investigators per the protocol). The hypothesis is that albuterol use will increase several days prior to a moderate or severe CE-COPD and can serve as a marker of COPD deterioration.

The endpoints of the trial are the primary outcome measure (ie, CE-COPD) and the primary outcome predictor (ie, albuterol use) alone or in combination with secondary predictors (ie, other study data). These predictors of CE-COPD will be modeled to determine which patterns best predict the subsequent development of CE-COPD.

For albuterol use, parameters of interest will include (1) the total number of inhalations in the days preceding the peak of a CE-COPD, (2) the number of days prior to the peak of a CE-COPD when albuterol use increased, and (3) the number of albuterol uses in the 24 hours preceding a CE-COPD. Therefore, endpoints are not designated as either primary or secondary.

In addition to albuterol use, inspiratory flow values (maximal inhalational flow (MIF), inhalational volume, inhalation duration, and time to MIF), sleep disruption index (SDI), total daily steps (TDS), and baseline information regarding disease state and demographics will be studied. These data will be analyzed using both a univariate and multivariate approach, to determine which patterns best predict the subsequent development of a CE-COPD. Inspiratory flow values are obtained from the eMDPI, SDI is obtained for a subset of patients who agree to participate at specific investigational centers (n=100) from an accelerometer worn on the wrist, and TDS is obtained for a subset of patients who agree to participate at specific investigational centers (n=100) from an accelerometer worn on the ankle. Baseline disease state and demographic information will be obtained at screening.

Another objective for this study is to evaluate the safety of ABS eMDPI use in patients with exacerbation-prone COPD.

The safety endpoints for this study include the following:

- adverse event data
- physical examinations

2. STUDY DESIGN

2.1. General Design

This is a 12-week, multicenter, open-label study to evaluate the relationship between as-needed usage of ABS eMDPI and CE-COPD in adult patients at least 40 years of age with exacerbation-prone COPD. ABS eMDPI is a rescue/reliever agent that includes an eModule on top of the approved PROAIR[®] RESPICLICK inhaler. The on-board electronics and power source are fully integrated into the inhaler and are designed to operate for the life of the inhaler without intervention. The electronic module records timestamped, pre-defined events such as cap open and inhalation parameters. The inclusion of the eModule has been shown to have no impact on the dose delivery compared with the approved product without the eModule.

The study will consist of a screening period of up to 2 weeks and a 12-week intervention period.

After providing written informed consent, patients will complete a screening visit (visit 1) to determine eligibility for the study. Patients will provide medical history (including prior medications), complete a physical examination, pregnancy test, if applicable, and review COPD exacerbation history. Eligible patients will return to the investigational center within 2 weeks for the baseline visit (visit 2). Those meeting entry criteria will be trained on the use of the eMDPI device and, upon demonstrated competency, will receive ABS eMDPI devices for use as rescue bronchodilators during the study. The screening visit and baseline visit may be combined.

Patients must use ABS eMDPI as their only rescue agent for the duration of their participation in this study and will be advised to place any current rescue pills, inhalers, or nebulizers, including SABA, short-acting muscarinic antagonists (SAMAs), or SABA/SAMA combination into storage. Patients may continue the use of other COPD and non-COPD medications as advised by their physician without changes unless deemed necessary by their physician. Patients will be managed according to routine clinical practice by their treating physician with no specific study-related instructions provided other than those on the proper use of ABS eMDPI.

Patients will be contacted by phone on a monthly basis for the collection of information about COPD exacerbations and treatments, concomitant medications, and adverse events. A review of the instructions for the use of ABS eMDPI and the procedure for replacement and return of ABS eMDPI will also occur during the monthly call.

Patients will receive initial eMDPI devices at visit 2 based on anticipated usage pattern. In the event that additional eMDPI devices are needed, patients will be required to visit the investigational center to receive them. Patients will be instructed to return all inhalers to the investigational center at the last study visit or earlier, including at the early termination visit, as well as at any other point if there is a problem with the inhaler. At the last study visit or early termination, patients will be queried for adverse events, concomitant medications, and COPD exacerbations; a physical examination will be completed; and the patient will subsequently be discharged from the trial.

Two subsets of patients who agree to participate at specific investigational centers and wear an accelerometer either on the ankle to measure TDS (n=100) or on the wrist to measure SDI (n=100) will be instructed on the proper use of these devices at the baseline visit (visit 2). The

devices will be worn throughout the 12-week intervention period and will be returned to the investigational center at the final visit or upon early termination (visit 5).

The end of study is defined as the last visit of the last patient.

The study duration will be approximately 9 months.

Study procedures and assessments with their timing are summarized in [Table 1](#) of the study protocol.

Table 1: Study Procedures and Assessments

Study period	Pre-intervention		Intervention			
	V1	V2	V3 ^a	V4 ^a	Vz	V5
Day and allowed time windows	Day -14 to Day 1	Day 1	Day 28 ±7 days	Day 56 ± 7 days	Up to 14 days after CE-COPD start date	Day 84 ±14 days
Procedures and assessments	Screening	Baseline	Phone visit	Phone visit	Exacerbation visit	Final/early termination visit
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Assign patient number	X					
Medical history	X					
Prior medication and treatment history	X					
Physical examination, including height and weight ^b	X				X	X
Vital signs measurement ^c	X					
Urine pregnancy test for women of childbearing potential	X					X
Inform patients of study compliance for eMDPI and accelerometer and requirement for provider visit in the event of CE-COPD	X	X	X	X		
Assess for COPD exacerbations	X	X	X	X		X
Adverse events inquiry		X	X	X	X	X
Wearable accelerometers: dispense, training, and collection ^d		X				X
ABS eMDPI: dispense, training, collection, and accountability ^e		X			X	X
Concomitant medication inquiry	X	X	X	X	X	X

^a Investigational centers must obtain source documentation for all COPD exacerbations that occur during the treatment period to confirm the accuracy of the information obtained from the patient.

^b Height will be measured at the screening visit only.

^c Vital signs measurements will include blood pressure, respiratory rate, and heart rate.

^d Wearable accelerometers for a subset of patients who agree to participate at specific investigational centers will be dispensed at visit 2, and SDI and TDS data will be collected continuously from visit 2 through visit 5 via the wearable accelerometer. Instructions for proper use of the devices will be provided to patients at visit 2. The devices will be collected at visit 5.

^e Patients will receive initial eMDPI devices at visit 2 based on anticipated usage pattern. In the event that additional eMDPI devices are needed, patients will be required to visit the investigational center to receive them. Patients will be instructed to return all inhalers to the investigational center at the last study visit or earlier, including at the early termination visit, as well as at any other point if there is a problem with the inhaler. Instructions for dispensing, proper clinical use, and collecting ABS eMDPI will be provided to patients at visit 2 and reviewed during the monthly calls.

ABS = albuterol sulfate; CE-COPD = clinical exacerbation of chronic obstructive pulmonary disease; COPD= chronic obstructive pulmonary disease; eMDPI=multidose dry powder inhaler with an eModule; SDI = sleep disruption index; TDS=total daily step; V = visit.

Note: Screening and baseline visits may be combined.

2.1.1. Treatment

2.1.1.1. Investigational Medicinal Products Used in the Study

Patients will receive initial eMDPI devices at visit 2 based on anticipated usage pattern and return all inhalers to the investigational center at the last study visit or earlier, including at the early termination visit (visit 5), as well as at any other point if there is a problem with the inhaler.

2.1.1.2. Test Investigational Medicinal Product

ABS eMDPI is an inhalation-driven MDPI containing a blend of ABS and alpha-lactose monohydrate. The inhaler contains 200 actuations, each delivering 90 mcg of albuterol base ex-mouthpiece; the inhaler is equipped with a dose counter that shows only even numbers and counts down to “0”.

Additional details may be found in Table 2 of the protocol.

2.1.1.3. Starting Dose and Dose Levels

The prescribed dose will be 90 mcg, 1 to 2 inhalations every 4 hours as needed. No dose escalations are planned.

2.2. Randomization and Blinding

This is a nonrandomized study. All patients will use the 1 Test investigational medicinal product (IMP), the ABS eMDPI. Blinding is not applicable.

2.3. Sample Size and Power Considerations

Assuming an expected dropout rate of 10%, it is recommended that 400 patients be enrolled so that 360 evaluable patients complete the study. These conclusions are based on a review of the relevant literature, as follows.

Based on previous studies of an exacerbation-prone COPD cohort ([Dransfield et al 2013](#), [Vogelmeier et al 2011](#), [Wedzicha et al 2013](#), [Wedzicha et al 2016](#)), it is expected that 91 (range, 73 to 110) CE-COPD events will occur over the 12-week evaluation period in this study based on reported CE-COPD exacerbation rates of 1.05 and 1.14 events per year. Furthermore, it is expected that 14% (14) of total exacerbations will be severe.

This sample size (ie, n=400 patients, 73 to 110 CE-COPD events) is considered adequate for the fulfillment of the study objectives to evaluate the relationship of albuterol use, inspiratory flow, SDI, and TDS data associated with a subsequent CE-COPD event. Per a previous study ([Jenkins et al 2013](#)), a statistically significant relationship was established between daily SABA usage and subsequent CE-COPD.

In the present study, approximately 73 to 110 CE-COPD events are desired because the model's fitting of the current study involves the analysis of multiple predictors as described in more detail below. Because the largest model considered has 7 covariates, it is desirable to have at least 70 events. The probability to observe at least 70 CE-COPD events is higher than 0.99.

Risk models published in the literature have typically included between 4 and 6 covariates/risk factors ([Bateman et al 2015](#), [Greenberg et al 2012](#), [Quezada et al 2016](#)) to examine the relationship between possible risk factors and a disease. When there is more than 1 covariate (risk factor) in the model, multiple logistic regression may be used to estimate the relationship of a specific covariate of interest (ie, albuterol use) to a primary outcome (ie, CE-COPD), adjusting for the other/remaining covariates (risk factors). In this case, the required sample size to estimate such a relationship is greater than that for univariate logistic regression.

The number of events per variable has been suggested as a criterion for the size of a data set ([Harrell et al 1984](#), [Laupacis et al 1997](#), [Peduzzi et al 1996](#),). The rule of thumb when building logistic regression models is 1 predictor variable for every 10 events ([Peduzzi et al 1996](#), [Vittinghoff and McCulloch 2007](#)). Therefore, this sample size would be adequate for predicting the primary outcome (CE-COPD) using multiple logistic regression, including the covariate of primary interest (ie, albuterol use) and the remaining multiple predictors (inspiratory flow values, SDI, and TDS) as potential risk factors for CE-COPD in the model for this patient population.

2.4. Sequence of Planned Analyses

2.4.1. Planned Interim Analyses

There will be no formal interim analysis for this study.

2.4.2. Final Analyses and Reporting

All analyses identified in this Statistical Analysis Plan will be performed after the end of the study as defined in the study protocol.

Data used for final statistical analyses will be derived from various sources including eCRF, data from ABS eMDPI inhaler, wrist, and ankle accelerometers.

This Statistical Analysis Plan and any corresponding amendments will be approved before database lock, in accordance with SOP GBP_RD_702 (Statistical Analysis Plan).

3. ANALYSIS SETS

3.1. Intent to Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all enrolled patients regardless of whether a patient took any IMP. A patient is considered enrolled according to the status reported in the database. This analysis set will be used for endpoint analysis and safety analysis.

3.2. Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set that will include patients who used the IMP at any time during the study and patients who did not use the IMP at any time during the study provided these patients complied with study requirements and the data from the ABS eMDPI inhalers were successfully downloaded at the end of the study.

3.3. Safety Analysis Set

The safety analysis set will include all enrolled patients who received at least 1 dose of the IMP.

3.4. Wrist Accelerometry Analysis Set

The wrist accelerometry analysis set is a subset of the mITT analysis set that will include patients who wore a wrist accelerometer with sufficient memory to capture 12 weeks of data during study participation and for whom data from the wrist accelerometer were successfully downloaded at the end of the study.

3.5. Ankle Accelerometry Analysis Set

The ankle accelerometry analysis set is a subset of the mITT analysis set that will include patients who wore an ankle accelerometer with sufficient memory to capture 12 weeks of data during study participation and for whom data from the ankle accelerometer were successfully downloaded at the end of the study.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n (number), mean, standard deviation (SD), median, minimum, and maximum. Minimum and maximum will have the same number of decimal points as the original data. Mean and median will have 1 more decimal point than the original data. Reporting of SD will have 2 more decimal points than the original data.

Descriptive statistics for categorical variables include patient counts and/or counts and percentages. Categories for missing data will be presented, if necessary. Confidence intervals (CIs) of means and/or proportions will be reported as specified. Summaries will be provided overall and by CE-COPD status (CE-COPD: No, CE-COPD: Yes, All) and by COPD severity (Yes: Moderate, Yes: Severe) where appropriate.

4.2. Specification of Baseline Values

4.2.1. Albuterol Use

Baseline albuterol use is defined as the mean number of inhalations per day from day 1 to day 7. If no inhalations were taken during study day 1 through study day 7, the 'baseline inhalation' is the first available inhalation after study day 7. For analyses relative to baseline albuterol use, patients who had a CE-COPD during study day 1 through study day 7 will be excluded.

4.2.2. Vital Signs, Physical Examination, Height, and Weight

Baseline vital signs (systolic blood pressure, diastolic blood pressure, respiratory rate, and heart rate (pulse rate), physical examination, height, and weight are performed only at Screening. Given the screening and baseline visits can be combined, baseline vital signs, physical examination, height, and weight are those assessments performed during the Screening visit.

4.2.3. Inhalational Flow Values

The baseline inspiratory flow values are computed using the set of inhalations taken by the patient during study day 1 through day 7. Among these inhalations, the inhalation with the highest MIF value is considered the 'baseline inhalation'. The baseline MIF, inhalational volume, inhalation duration, and time to MIF values are those of the identified 'baseline inhalation'. If no inhalations were taken during study day 1 through study day 7, the 'baseline inhalation' is the first available inhalation after study day 7.

4.2.4. Total Daily Steps

Baseline TDS is the average number of daily steps a patient completes, computed using the daily steps recorded during the first 7 days of study participation (study day 1 through study day 7). The average will be calculated as the sum of the daily TDS divided by the number of days with nonmissing TDS. If no step data are available for study day 1 through study day 7, the 'baseline TDS' is the first available TDS after study day 7.

Baseline TDS are computed for those patients in the ankle accelerometry analysis set.

4.2.5. Sleep Parameters

There are 8 measures of sleep disruption: (i) nighttime average total time in bed, (ii) nighttime average total sleep time, (iii) nighttime average sleep latency time, (iv) nighttime average wakening after sleep onset, (v) total time awake at night, (vi) daytime average minutes asleep, (vii) longest daytime sleep episode and (viii) longest nighttime wake episode. The first 7 sleep parameters are provided via Philips accelerometry and longest nighttime wake episode is derived from the accelerometry data as follows:

The sleep interval data provided via Philips accelerometry includes the activity state ("sleep"/"awake") every 30 seconds during the sleep interval. The number of successive 30 second "awake" states occurring between "sleep" states within the sleep interval is summed to determine the duration of a given "awake" state. The longest nighttime wake episode is the summated "awake" state with the longest duration during the sleep interval.

The baseline value of a given sleep parameter (eg, nighttime average total time in bed) is the average sleep parameter (eg, nighttime average total time in bed), computed using the sleep parameter (eg, nighttime average total time in bed) values captured by accelerometry during study day 1 through day 7. The average will be calculated as the sum of the average sleep parameter divided by the number of days with nonmissing values of the average sleep parameter. If no sleep parameter data are available for study day 1 through study day 7, the 'baseline value of a given sleep parameter' is the first available valid sleep parameter value after study day 7.

Baseline sleep parameters are computed for those patients in the wrist accelerometry analysis set.

4.3. Time on Study

Time on study is the number of days from date of informed consent to date of completion or last contact date plus 1.

4.4. eMDPI Time on Study

The eMDPI time on study is the number of days (D_{emdpi}) from the last device return date to the date the first ABS eMDPI device was dispensed. For instances where the last device return date is missing the patient's last date of contact or study completion, date will be used, whichever comes first.

4.5. Study Day and Study Week

Study days will be numbered relative to the earliest date an ABS eMDPI device was dispensed (ie, ... -2, -1, 1, 2, ...). Day 1 is defined as the earliest date an ABS eMDPI device was dispensed and Day -1 is the day before the first ABS eMDPI device was dispensed.

Week I is defined as study day $(j + 1)$ to study day $(j + 7)$, inclusive where $I = 1$ to 12 and $j = 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84$, respectively.

4.6. Handling Withdrawals and Missing Data

Any data that was collected prior a patient's withdrawal from the study will be used for analysis and presented in the data listings.

The following imputation rules will be used;

- If the return date of the last ABS eMDPI device returned is missing the patient's last date of contact if the patient withdrew from the study or the patient's study completion date will be used as the return date (see Section 4.4 and Section 10.2).
- Adverse events or serious adverse events with missing start dates will be considered treatment emergent (see Section 10.4).
- If a patient never used the ABS eMDPI during the study or download of a given ABS eMDPI device was not successful, study day and weekly inhalational flow values will be missing. If download of a given wrist or ankle accelerometer was not successful, TDS and SDI indices will be missing. These missing data will not be imputed.
- In the derivation of Study Day X Inhalation flow values, if there was no albuterol use on Study Day X , then the closest preceding nonmissing Study Day Inhalation is used as the 'Study Day X Inhalation' and the inhalational flow values for Study Day X are assigned accordingly (see Section 7.2.1).
- For patients in the ankle accelerometry analysis set, if no step data are available for study day 1 through study day 7, the 'baseline TDS' is the first available TDS after study day 7 (see Section 4.2.4).
- For patients in the wrist accelerometry analysis set, if no sleep parameter data are available for study day 1 through study day 7, the 'baseline value of a given sleep parameter' is the first available valid sleep parameter value after study day 7 (see Section 4.2.5).
- In the derivation of Study Day X TDS if TDS are missing on Study Day X , then the average of the nonmissing TDS of the 7 days preceding Study Day X is computed and assigned to Study Day X TDS (see Section 7.3.1).
- In the derivation of Study Day X nighttime average sleep latency time if nighttime average sleep latency time is missing on Study Day X , then the average of the nonmissing nighttime average sleep latency time of the 7 days preceding Study Day X is computed and assigned to Study Day X (see Section 7.4.1).
- In the derivation of Study Day X longest nighttime wake episode if longest nighttime wake episode is missing on Study Day X , then the greatest nonmissing longest nighttime wake episode of the 7 days preceding Study Day X is computed and assigned to Study Day X (see Section 7.4.1).
- In the derivation of Study Day X total time awake at night if total time awake at night is missing on Study Day X , then the average of the nonmissing total time awake at night of the 7 days preceding Study Day X is computed and assigned to Study Day X (see Section 7.4.1).

5. STUDY POPULATION

5.1. General

The ITT analysis set will be used for all study population summaries unless otherwise specified. The data will be listed for all patients entered into the database.

5.2. Patient Disposition

Data from patients screened; patients who were screen failures; patients who re-screened; patients screened but not enrolled and reason for non-enrollment; patients who are enrolled; patients enrolled but who do not use ABS eMDPI at least once; patients in the ITT analysis set; patients in the ankle accelerometry cohort and patients in the wrist accelerometry cohort; patients who complete the study; and patients who withdraw from the study and the reason for withdrawal will be summarized using descriptive summary statistics (n, %) for all patients entered into the database.

5.3. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics will be summarized for all patients in the ITT analysis set using descriptive statistics. Demographic and baseline characteristics will include: age, sex, race, ethnicity, weight, height, and body mass index (BMI), vital signs, TDS, inhalational flow values and SDIs.

The formula for BMI is: $BMI = \frac{\text{weight}}{\text{height}^2}$,

where weight is in kilograms (kg), height in meters (m) and BMI is kg/m².

Baseline inhalational flow values include MIF, inhalational volume, inhalation duration, and time to MIF. Baseline SDIs include nighttime average total time in bed, nighttime average total sleep time, nighttime average sleep latency time, nighttime average waking after sleep onset, total time awake at night, daytime average minutes asleep, longest daytime sleep episode and longest nighttime wake episode.

Demographics and baseline characteristics will be summarized by analysis set (ITT analysis set and the ankle and wrist accelerometry analysis sets).

5.4. Medical History

All medical history will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term (PT). Patients are counted only once in each PT and SOC category even if they have multiple applicable findings.

Summaries will be provided for the ITT analysis set and the ankle and wrist accelerometry analysis sets.

5.5. COPD History

Patients' COPD history data will be summarized. This will include duration of COPD.

Summaries will be provided for the ITT analysis set and the ankle and wrist accelerometry analysis sets.

5.6. Clinical COPD Exacerbations History

Patients' COPD exacerbations history data will be summarized. This will include COPD exacerbations in the past 12 months or previous year, hospitalizations, emergency room visits, urgent care, doctor visits for COPD exacerbations, ICU admissions, and systemic steroids administration for COPD.

Summaries will be provided for the ITT analysis set and the ankle and wrist accelerometry analysis sets.

5.7. Prior Therapy and Medication

All prior medications will be coded using the most current version of the World Health Organization drug dictionary (WHO Drug) at the time of database lock. The incidence of prior medications will be summarized using descriptive statistics (count and percentages) by therapeutic class and PT term. In addition, a summary table of the incidence of prior COPD medications will be provided. Patients are counted only once in each therapeutic class category, and only once in each PT term category. Prior medications will include medications taken within 30 days prior to the first day that IMP is dispensed.

Summaries will be provided for the ITT analysis set and the ankle and wrist accelerometry analysis sets.

5.8. Childbearing Potential and Methods of Contraception

Information related to childbearing potential, contraception, and menopause will be collected at Screening and at the Final/Early Termination visit. All information for childbearing potential will be provided in a listing by patient.

5.9. Study Protocol Violations

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered a protocol violation. Protocol violations include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary outcome measure criteria, or good clinical practice (GCP) guidelines; noncompliance to study drug administration; use of prohibited medications; or any other deviations that may have an impact on the processes put in place for the care and safety of the patients.

Protocol violations recorded in the Clinical Trial Management System during the study will be summarized overall and for each of the following categories using descriptive statistics:

- Informed Consent Procedures

- Inclusion/Exclusion Criteria
- Concomitant Medications/Therapy
- Lab Assessments/Procedures
- Study Procedures
- Serious Adverse Events
- Randomization Procedures/Dosing
- Visit Schedule/Interval

Of note, any recorded ‘Randomization Procedures/Dosing’ violations related to medication errors, overdose, misuse, abuse, off-label use and occupational exposure will be summarized in the sub-category ‘Non-compliance to study medication’.

Patients with at least 1 protocol violation will be summarized by the above categories (sub-categories) using count and percentages, by analysis set (ITT analysis set, and the ankle and wrist accelerometry analysis sets).

5.10. eMDPI Time on Study; Days and Weeks

Summary statistics of the eMDPI time on study in days and weeks (days divided by 7) will be presented overall and by CE-COPD status and by CE-COPD severity (Yes: severe, moderate; No) for the ITT analysis set, ankle accelerometry analysis set and the wrist accelerometry analysis set.

6. EFFICACY ANALYSIS

Efficacy will not be assessed in this study. Endpoint analyses are described in Section [7](#).

7. ENDPOINT ANALYSES

All endpoint analyses will be performed using the ITT analysis set.

Data listings will be presented by patient.

7.1. eMDPI: Albuterol Use

7.1.1. Albuterol Use Definition

Baseline albuterol use is defined as the mean number of inhalations per day from day 1 to day 7. If no inhalations were taken during study day 1 through study day 7, the 'baseline inhalation' is the first available inhalation after study day 7. For analyses relative to baseline albuterol use, patients who had a CE-COPD during study day 1 through study day 7 will be excluded.

Week 1 Patient Albuterol Use: Week 1 patient albuterol use is each patient's total number of albuterol inhalations taken and the number of days used during the first week (study day 1 through study day 7) of study participation with an indicator of whether or not the most frequent daily usage of albuterol is in 1 of the following 3 categories: (a) 0 to 2 inhalations, (b) 3-6 inhalations and (c) > 6 inhalations. It is presented as WK1:I#iD#dMTN#n, where "i" is the number of albuterol inhalations and "d" is the number of days used in the first 7 days of the study, and "n" is an indicator of whether or not the most frequent daily usage of albuterol falls into one of the 3 categories. If there is a tie in the most frequent daily usage, the category with the highest number of inhalations will be reported. For example, "I28D7MTN2" indicates a total of 28 inhalations were taken, albuterol use was used each of the 7 days and the highest most frequent usage per day falls into category 2 with 3-6 inhalations.

Week 2 Patient Albuterol Use: Week 2 patient albuterol use is each patient's total number of albuterol inhalations taken and the number of days used during the second week (study day 8 through study day 14) of study participation with an indicator of whether or not the most frequent daily usage of albuterol is in one of the following 3 categories: (a) 0 to 2 inhalations, (b) 3-6 inhalations and (c) > 6 inhalations. It is presented as "WK2:I#iD#dMTN#n", where "i" is the number of albuterol inhalations and "d" is the number of days used in the second week of study, and "n" is an indicator of whether or not the most frequent daily usage of albuterol is in one of the 3 categories. If there is a tie in the most frequent daily usage, the category with the highest number of inhalations will be reported.

14-Day Patient Albuterol Use: 14-day patient albuterol use is each patient's total number of albuterol inhalations taken and the number of days used during the first 14 days (study day 1 through study day 14) of study participation with an indicator of whether or not the most frequent daily usage of albuterol is in one of the following 3 categories: (1) 0 to 2 inhalations, (2) 3-6 inhalations and (3) > 6 inhalations. It is presented as "D14:I#iD#dMTN#n", where "i" is the number of albuterol inhalations and "d" is the number of days used in the first 14 days of study, and "n" is an indicator of whether or not the most frequent daily usage of albuterol is in one of the 3 categories. If there is a tie in the most frequent daily usage, the category with the highest number of inhalations will be reported.

Albuterol use will be examined by the following 3 parameters; (i) total number of inhalations in the days preceding the peak of a CE-COPD, (ii) number of days prior to the peak of a CE-COPD when albuterol use increased, and (iii) number of albuterol uses in the day preceding a CE-COPD.

The maximum number of inhalations taken within a 24-hour period by each patient: The date and time stamp of the inhalations are taken into consideration when determining the maximum number of inhalations taken within a 24-hour period by each patient. For patients who experienced a CE-COPD, the maximum number of inhalations taken within a 24-hour period is determined among the days prior to the date of the symptom peak of the exacerbation.

7.1.2. Analysis Methods for Albuterol Use

7.1.2.1. Pattern of Baseline Daily and Weekly Albuterol Use

A patient's pattern of baseline albuterol use is exhibited if, on any given day, during a given week, they do not take more than their average number of inhalations computed from day 1 to day 7.

Summary statistics including 95% CIs intervals of the proportion of patients exhibiting their individual weekly baseline albuterol use during each week of the 12 week study (Week 1, Week 2,..., Week 12) will be presented overall and by CE-COPD status and by CE-COPD severity (Yes: severe, moderate; No).

Summary statistics including 95% CIs intervals of the proportion of eMDPI time on study days when a patient did not take more than the average number of inhalations computed from day 1 to day 7 (number of days a given patient had no more than average baseline albuterol use) / total number of eMDPI study days for a given patient) will be summarized overall and by CE-COPD status and by CE-COPD severity (Yes: severe, moderate; No).

Week 1 and Week 2 and the first 14 day patient albuterol use patterns, "WK1:I#iD#dMTN#n," "WK2:I#iD#dMTN#n" and "D14:I#iD#dMTN#n" designation, will be summarized descriptively (counts and percent) overall and by CE-COPD status and by CE-COPD severity (Yes: severe, moderate; No).

7.1.2.2. Total Number of Inhalations in the Days Preceding the Peak of a CE-COPD

For patients who experienced a CE-COPD, summary descriptive statistics of the total number of inhalations taken in 1 day (eg, the 24-hour period on the day prior to the date of the CE-COPD symptom peak) and at 3, 5, 7, 10, 14, and 21 days preceding the date of the CE-COPD symptom peak, will be presented overall and by moderate CE-COPDs and severe CE-COPDs.

In this analysis, among patients experiencing more than 1 CE-COPD, the subsequent CE-COPDs can be considered a separate CE-COPD, distinct from the first (preceding) CE-COPD, provided the patient exhibited at least 1 day of baseline albuterol use after the first (preceding) CE-COPD's end date, as captured on the adverse event page, and prior to the subsequent CE-COPD's start date, as captured on the adverse event page. For patients who experience multiple CE-COPDs, all distinct CE-COPDs will be considered in this descriptive analysis. Descriptive summaries of the number of inhalations on the days prior to a CE-COPD will only be reported if the event does not overlap with a preceding CE-COPD. For example, if the date of symptom

peak for a patient's second CE-COPD occurs 12 days after the end date of the patient's first CE-COPD and there is at least 1 day of baseline albuterol use between these dates, then only the data collected on 1, 3, 5, 7, and 10 days (not 14 and 21 days) prior to the second CE-COPD will be included when computing the summaries measures.

Mean and 95% CIs of the total number of inhalations per day, for each eMDPI study day, will be summarized graphically. The number of patients contributing to the summary statistics at Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84 will also be presented. Three line graphs will be presented in 1 figure: "Overall" and by "CE-COPD Status" (Yes, No). Three line graphs will be presented in a second figure; "CE-COPD Status No", "CE-COPD Status Yes: Severe" and "CE-COPD Status Yes: Moderate".

A figure summarizing the mean (+/- minimum and maximum) of the total number of inhalations per day, for each patient experiencing multiple CE-COPDs, will be presented for the time period of 21 days prior to the date of symptom peak of the first CE-COPD to 21 days after the date of symptom peak of the last CE-COPD. The x-axis will be labeled -21, -20, ..., -1, 0, 1, 2, ... D , where day 0 is the date of symptom peak of the first CE-COPD and D is the study day number 21 days after the date of the symptom peak of the last CE-COPD.

7.1.2.3. Hypothesis: Albuterol Use Will Increase Several Days Prior to a CE-COPD

The hypothesis under consideration is that albuterol use will increase several days prior to a CE-COPD. Several days will be defined as 7 days prior to the date of the CE-COPD symptom peak for this analysis.

For each subject that experiences at least 1 CE-COPD, Y_1, \dots, Y_7 will represent the number of puffs of albuterol during the 7 days preceding the date of the CE-COPD symptom peak and Y_8, \dots, Y_{14} will represent the number of puffs taken each day during days 8 through 14 preceding the date of the CE-COPD symptom peak. Under the hypothesis of no increased albuterol use

preceding an exacerbation (ie, null hypothesis) assume for subject "xxx" that $Y_i \stackrel{iid}{\sim} Poisson(\lambda_{xxx})$ for all subjects i . Alternatively, if albuterol use does increase prior to an exacerbation, then

$Y_i \stackrel{iid}{\sim} Poisson(\lambda_{xxx})$ during day 8 through 14 preceding the date of the CE-COPD symptom peak

and $Y_i \stackrel{iid}{\sim} Poisson(\lambda_{xxx} + \delta)$ for the immediate 7 days preceding the CE-COPD(s). Also, for

random subject effect, assume λ_{xxx} follows some distribution to account for subject to subject variability. Let d_{xxx} will equal to the mean number of puffs during the 7 days immediately preceding the date of the CE-COPD symptom peak minus mean number of puffs during days 8 through 14 preceding the date of the CE-COPD symptom peak. To assess if albuterol usage increases 7 days prior to a CE-COPD, $H_0: \mu_D = 0$, $H_1: \mu_D > 0$ will be tested using a t-test at the 0.05 significance level.

7.1.2.4. Number of Days Prior to the Peak of a CE-COPD When Albuterol Use Increased

Among patients who experienced a CE-COPD, summary statistics of the number of days prior to the peak of a CE-COPD when albuterol use increased, will be presented overall and by moderate CE-COPDs and severe CE-COPDs for 3 thresholds defining an increase in albuterol use;

- (i) First occurrence of a single day increase of 20% from baseline use prior to CE-COPD
- (ii) First occurrence of a single day absolute increase of 2 inhalations from baseline use prior to CE-COPD
- (iii) First occurrence of a single day absolute increase of 4 inhalations from baseline use prior to CE-COPD

Among patients who did not experience a CE-COPD, summary statistics, including 95% CIs intervals of the proportion of eMDPI time on study days when a patient exceeded a given threshold of albuterol use (number of days a given patient's single day's albuterol use exceeded 4 inhalations/total number of eMDPI study days for a given patient), will be summarized for 3 thresholds defining an increase in albuterol use;

- (i) First occurrence of a single day increase of 20% from baseline use
- (ii) First occurrence of a single day absolute increase of 2 inhalations from baseline use
- (iii) First occurrence of a single day absolute increase of 4 inhalations from baseline use

7.1.2.5. Maximum Number of Inhalations Taken In a 24-Hour Period

Summary descriptive statistics of the maximum number of inhalations taken in a 24-hour period will be presented overall and by CE-COPD status and by CE-COPD severity.

Data listings for each parameter of albuterol use will be presented by patient.

7.2. Inhalational Flow Values

7.2.1. Inhalational Flow Values Definitions

Study Day X and Week Y inhalational flow values are defined as follows:

Study Day X Inhalational Flow Values: The inhalational flow values for study day X are computed using the set of inhalations taken by the patient on study day X . Among these inhalations, the inhalation with the highest maximal MIF value is considered the 'Study Day X Inhalation'. The Study Day X MIF, inhalational volume, inhalation duration, and time to MIF values are those of the identified 'Study Day X Inhalation'. If there was no albuterol use on Study Day X , then the closest preceding nonmissing Study Day Inhalation' is used as the 'Study Day X Inhalation' and the inhalational flow values for Study Day X are assigned accordingly.

Week Y Inhalational Flow Values: The inhalational flow values for Week Y are computed using the set of inhalations taken by the patient during a given week on the study. Among these inhalations, the inhalation with the highest MIF value is considered the 'Weekly Y Inhalation'.

The Weekly *Y* MIF, inhalational volume, inhalation duration, and time to MIF values are those of the identified ‘Weekly *Y* Inhalation’.

Note, if a patient never used the ABS eMDPI during the study or download of a given ABS eMDPI device was not successful, study day and weekly inhalational flow values will be missing.

7.2.2. Analysis Methods for Inhalational Flow Values

7.2.2.1. Actual and Change from Baseline in Study Day *X* Inhalational Flow Values Prior to the Peak of a CE-COPD

Among patients who experienced a CE-COPD, summary descriptive statistics of the actual inhalational flow values and change from baseline in daily inhalational flow values for MIF, inhalational volume, inhalation duration, and time to MIF at 1 day (eg, the 24-hour period on the day prior to the date of the CE-COPD symptom peak) and at 3, 5, 7, 10, 14, and 21 days preceding the peak of a CE-COPD, will be presented for all CE-COPDs and by moderate CE-COPDs and severe CE-COPDs.

In this analysis, among patients experiencing more than 1 CE-COPD, the subsequent CE-COPDs will be considered a separate CE-COPD distinct from the first (preceding) CE-COPD, provided the patient exhibited at least 1 day of baseline albuterol use after the first (preceding) CE-COPD’s date of symptom peak and prior to the subsequent CE-COPD’s date of symptom peak. For patients who experience multiple CE-COPDs (eg, 3), for a given number of days preceding a CE-COPD (eg, 7 days), if the (eg, third) CE-COPD overlaps with the time period of the preceding (eg, second) CE-COPD, the CE-COPD (eg, third CE-COPD) should not be included in the analysis.

Summary descriptive statistics of the actual inhalational flow values and change from baseline in daily inhalational flow values for MIF, inhalational volume, inhalation duration, and time to MIF will be presented for overall, by CE-COPD status, by CE-COPD severity (Yes: severe, moderate; No) and for the first occurrence of a single day increase of 20% from baseline use. For patients who experienced a CE-COPD, the single day increase of 20% from baseline use is the single day increase of 20% from baseline use prior to the exacerbation.

In addition, summary descriptive statistics of the maximum change from baseline in daily inhalational flow values for MIF, inhalational volume, inhalation duration, and time to MIF, will be presented overall and by CE-COPD status and by CE-COPD severity (Yes: severe, moderate; No). For patients who experienced a CE-COPD, the maximum change from baseline is the maximum change prior to the exacerbation.

7.2.2.2. Actual and Change from Baseline in Week *Y* Inhalational Flow Values

Summary descriptive statistics of the actual inhalational flow values and change from baseline in MIF, inhalational volume, inhalation duration, and time to MIF for each study week (1 through 12) will be presented overall, and by CE-COPD status and by CE-COPD severity.

7.3. Accelerometry: Total Daily Steps

7.3.1. Total Daily Steps Definition

Study Day *X* and Week *Y* TDS are defined as follows:

Study Day *X* TDS: The TDS for study day *X* are the TDS recorded by accelerometry on study day *X*. If TDS are missing on Study Day *X*, then the average TDS of the 7 days preceding study day *X* is computed and assigned to Study Day *X*.

Week *Y* TDS: The TDS for Week *Y* are computed using the set of TDS taken by the patient during a given week on study. The average will be calculated as the sum of the daily TDS divided by the number of days with nonmissing TDS.

The TDS are computed for those patients in the ankle accelerometry analysis set.

7.3.2. Analysis Methods for Total Daily Steps

7.3.2.1. Actual and Change from Baseline in Study Day *X* Total Daily Steps Prior to the Peak of a CE-COPD

Among patients in the ankle accelerometry cohort who experienced a CE-COPD, summary descriptive statistics of the actual TDS and change from baseline in TDS 1 day (eg, the 24-hour period on the day prior to the date of the CE-COPD symptom peak) and at 3, 5, 7, 10, 14, and 21 days preceding the peak of a CE-COPD, will be presented for all CE-COPDs and by moderate CE-COPDs and severe CE-COPDs.

In this analysis, among patients experiencing more than 1 CE-COPD, the subsequent CE-COPDs will be considered a separate CE-COPD distinct from the first (preceding) CE-COPD provided the patient exhibited at least 1 day of baseline albuterol use after the first (preceding) CE-COPD's date of symptom peak and prior to the subsequent CE-COPD's date of symptom peak. For patients who experience multiple CE-COPDs (eg, 3), for a given number of days preceding a CE-COPD (eg, 7 days), if the (eg, third) CE-COPD overlaps with the time period of the preceding (eg, second) CE-COPD, the CE-COPD (eg, third CE-COPD) will not be included in the analysis.

Among patients in the ankle accelerometry cohort, summary descriptive statistics of the actual TDS and change from baseline in TDS, will be presented for overall, by CE-COPD status, by CE-COPD severity (Yes: severe, moderate; No) and for the first occurrence of a single day increase of 20% from baseline use. For patients who experienced a CE-COPD, the single day increase of 20% from baseline use is defined as the single day increase of 20% from baseline use prior to the exacerbation.

In addition, summary descriptive statistics of the maximum change from baseline in TDS will be presented overall and by CE-COPD status and by CE-COPD severity. For patients who experienced a CE-COPD, the maximum change from baseline in TDS is the maximum change from baseline in TDS during the days prior to the exacerbation.

7.3.2.2. Actual and Change from Baseline in Week Y Total Daily Steps

Summary descriptive statistics of the actual Week Y TDS and change from baseline in TDS for each study week (1 through 12) will be presented overall, and by CE-COPD status and by CE-COPD severity (Yes: severe, moderate; No) using the ankle accelerometry analysis set.

7.4. Accelerometry: Sleep Disruption Index

7.4.1. Sleep Disruption Index Definition

The SDI for analysis in this study will consist of the following measures, which correlate significantly with SABA rescue use (Krouse et al. 2008) and the composite score derived from the summation of these 3 measures.

- (i) Nighttime Average Sleep Latency Time ($r=0.78$)
- (ii) Longest Nighttime Wake Episode ($r=0.73$)
- (iii) Total Time Awake at Night ($r=0.65$)

Study Day X and Week Y SDIs are defined as follows:

Study Day X Nighttime Average Sleep Latency Time: The nighttime average sleep latency time for study day X is the nighttime average sleep latency time recorded by wrist accelerometry on study day X . If nighttime average sleep latency time is missing on Study Day X , then the average nighttime average sleep latency time of the 7 days preceding study day X is computed and assigned to Study Day X .

Week Y Nighttime Average Sleep Latency Time: The nighttime average sleep latency time for Week Y is computed using the set of nighttime average sleep latency times recorded by wrist accelerometry during a given week on study. The average will be calculated as the sum of the daily nighttime average sleep latency times divided by the number of days with nonmissing nighttime average sleep latency times.

Study Day X Longest Nighttime Wake Episode: The longest nighttime wake episode for study day X is the longest nighttime wake episode calculated as described in Section 4.2.5 on study day X . If longest nighttime wake episode is missing on Study Day X , then the greatest longest nighttime wake episode of the 7 days preceding study day X is computed and assigned to Study Day X .

Week Y Longest Nighttime Wake Episode: The longest nighttime wake episode for Week Y is the greatest longest nighttime wake episode calculated as described in Section 4.2.5 during a given week on study.

Study Day X Total Time Awake at Night: The total time awake at night for study day X is the total time awake at night time recorded by wrist accelerometry on study day X . If total time awake at night is missing on Study Day X , then the average total time awake at night of the 7 days preceding study day X is computed and assigned to Study Day X .

Week Y Total Time Awake at Night: The total time awake at night for Week Y is computed using the set of total time awake at night times recorded by wrist accelerometry during a given week on study. The average will be calculated as the sum of the total time awake at night times divided by the number of days with nonmissing total time awake at night times.

Study Day X SDI Composite Score: The SDI composite score for study day X is sum of nighttime average sleep latency time, longest nighttime wake episode and total time awake at night on study day X .

Week Y SDI Composite Score: The SDI composite score for Week Y is the sum of nighttime average sleep latency time, longest nighttime wake episode and total time awake at night for Week Y .

The SDIs are computed for those patients in the wrist accelerometry analysis set.

7.4.2. Analysis Methods for Sleep Disruption Indices

7.4.2.1. Actual and Change from Baseline in Study Day X Sleep Disruption Indices Prior to the Peak of a CE-COPD

Among patients in the wrist accelerometry cohort who experienced a CE-COPD, summary descriptive statistics of nighttime average sleep latency time, longest nighttime wake episode, and total time awake at night and change from baseline in these 3 measures of SDI at 1 day (eg, the 24-hour period on the day prior to the date of the CE-COPD symptom peak) and at 3, 5, 7, 10, 14 and 21 days preceding the peak of a CE-COPD, will be presented for all CE-COPDs and by moderate CE-COPDs and severe CE-COPDs.

Summary descriptive statistics of nighttime average sleep latency time, longest nighttime wake episode, and total time awake at night and change from baseline in these 3 measures of SDI will be presented for overall, by CE-COPD status, by CE-COPD severity (Yes: severe, moderate; No) and for the first occurrence of a single day increase of 20% from baseline use. For patients who experienced a CE-COPD, the single day increase of 20% from baseline use is defined as the increase prior to the exacerbation.

In addition, summary descriptive statistics of the maximum daily change from baseline nighttime average sleep latency time, longest nighttime wake episode, and total time awake at night, will be presented overall and by CE-COPD status and by CE-COPD severity. For patients who experienced a CE-COPD, the maximum daily change from baseline is the change prior to the exacerbation.

7.4.2.2. Actual and Change from Baseline in Week Y Sleep Disruption Indices

Summary descriptive statistics of the absolute Week Y nighttime average sleep latency time, longest nighttime wake episode, total time awake at night, and SDI composite score and change from baseline in these 4 SDIs for each study week (1 through 12), will be presented overall, and by CE-COPD status and by CE-COPD severity.

7.5. Clinical Exacerbation of COPD

7.5.1. Definition of Clinical Exacerbation of COPD

A CE-COPD is the primary outcome measure of this study. In this study, a CE-COPD is an occurrence of either a “severe CE-COPD” or a “moderate CE-COPD.” “Mild CE-COPD” is defined below for investigator information but is not used either for entry criteria or as a measure in this study.

- Severe CE-COPD is defined as an event that involves worsening respiratory symptoms for at least 2 consecutive days requiring treatment with systemic corticosteroids (SCS; at least 10 mg prednisone equivalent above baseline [Table 2]) and/or systemic antibiotics and a hospitalization for CE-COPD.
- Moderate CE-COPD is defined as an event that involves worsening respiratory symptoms for at least 2 consecutive days requiring treatment with SCS (at least 10 mg prednisone equivalent above baseline [Table 2]), and/or systemic antibiotics, and an unscheduled encounter (such as a phone call, an office visit, an urgent care visit, or an emergency care visit) for a CE-COPD, but not a hospitalization.
- Mild CE-COPD is defined as a worsening of respiratory symptoms for at least 2 consecutive days requiring self-management by the patient, such as increased inhaler use, but not requiring treatment with SCS and/or antibiotics, nor an unscheduled visit of any kind.

Table 2: Systemic Glucocorticoid Treatment Equivalent to 10 mg of Prednisone

Glucocorticoid Treatment	Dose (mg) Equivalent to 10 mg of Prednisone	Comment
Cortisone	50	Includes parenteral
Hydrocortisone	40	Cortisol
Prednisolone	10	-
Methylprednisolone	8	Medrol: includes parenteral SOLU-MEDROL®
Triamcinolone	8	-
Betamethasone	0.4	-
Dexamethasone	0.4	Oral or parenteral DECADRON®

The designation of a CE-COPD as moderate or severe is denoted by the response to the CRF question “Severity” on the Clinical Exacerbation of COPD CRF page regardless of whether the following CRF questions are answered in the negative or missing:

- “The treating physician elects to administer prednisone (or equivalent glucocorticoid treatment) at least 10 mg prednisone equivalent above baseline, for at least 3 days”
- An unscheduled provider visit such as an office visit, telephone call, urgent care visit, emergency care visit, or hospitalization

A patient may experience more than 1 CE-COPD during the study period.

Clinical Exacerbation of COPD Status: Clinical exacerbation of COPD status is an indicator of whether or not a patient experienced a CE-COPD during study follow-up (Yes, No).

Clinical Exacerbation of COPD Rate: The percentage of patients who experience at least 1 moderate or severe CE-COPD at the end of study follow-up.

Recurrent Clinical Exacerbation of COPD Rate: The percentage of patients who experience more than 1 moderate or severe CE-COPD at the end of study follow-up.

Time to Clinical Exacerbation of COPD: Time, in days, from Study Day 1 to the Date of Symptom Peak plus 1.

7.5.2. Analysis Methods for Clinical (COPD) Exacerbation

As specified in the protocol, because the device-use-measures will be collected continuously over time, these measures could be used to derive many potential predictors of risk. Several analyses are proposed to study correlations between CE-COPD and device-use-measures.

7.5.2.1. Within Patient CE-COPD Analyses

For each CE-COPD event occurring at least 2 weeks after baseline, device-use measures (albuterol use, inhalational flow [MIF], inhalational volume, and time to MIF) will be summarized for each of 2 weeks of interest: first- 'CE-COPD-adjacent week', the week immediately preceding the onset of CE-COPD symptom (ie, day 1 through 7 preceding the date of the CE-COPD symptom onset), and second – 'CE-COPD-Prior Adjacent week', the week preceding that week (ie, during day 8 through 14 preceding the date of the CE-COPD symptom onset). Summary measures of daily and or weekly use will be compared between the two weeks, as proposed below:

Albuterol use measures:

- total number of inhalations in that week
- the maximal daily number of inhalations in that week
- the mean number of daily inhalations (ie, total number of inhalations divided by number of days with number>0)
- occurrence of a single day's albuterol use exceeding 4 inhalations
- occurrence of a single day's albuterol use exceeding 8 inhalations
- occurrence of a single day's albuterol use exceeding 12 inhalations
- number of days when albuterol use exceeding 4 inhalations
- number of days when albuterol use exceeding 8 inhalations
- number of days when albuterol use exceeding 12 inhalations

To note, in this analysis, no inhalation in any day will be taken as a 0 count.

Inhalation flow values parameters:

- maximal daily MIF during the week
- minimal daily time to MIF within a week
- maximal total daily inhalational volume within a week

To note, if no inhalation was taken at a specific day, flow value parameters will be missing and will not be imputed.

Analysis will be based on all patients CE-COPDs for which there are 14 days (or more) prior to the CE-COPD onset, where patient has been on study and CE-COPD free.

Descriptive statistics of use measures in the 'CE-COPD-adjacent week' and 'CE-COPD-Prior Adjacent week' will be presented.

Continuous measures will be compared between the 2 weeks using paired t-test (and Wilcoxon Signed Ranks test) whereas binary patterns will be compared using Mc-Nemar test.

7.5.2.2. Time to Clinical (COPD) Exacerbations Short-term Exacerbation Risk (7 days)

For each patient, the following 3 landmark use events will be identified:

- first time in study when had >4 inhalations per day ("low use group")
- first time in study when had >8 inhalations per day ("medium use group")
- first time in study when had >12 inhalations per day ("high use group")

A patient may be included in more than 1 landmark use group (for example, if had >12 inhalations a day any time during study, then on that time or already before he/she also had >8 and >4 a day).

For each landmark use groups, time to CE-COPD within 7 days since the landmark event will be estimated and plotted using Kaplan-Meier plot. The 3 groups will be presented in the same plot, to assess a possible 'dose-response' association, if higher use is associated with shorter time to CE-COPD.

If a CE-COPD has not occurred within 7 days, then that observation will be censored at 7 days or earlier if follow-up had completed/terminated before 7 days elapsed. Note, if CE-COPD occurred on the same date where landmark use happened, then time to CE-COPD will be calculated as 0.

7.5.2.3. All Days Analysis (Only CE-COPD-free Days)

This analysis will be performed by the data analytics group. Additional details may be specified in a separate report. One possible analysis is presented below:

For each patient, all study days where the patient was CE-COPD free will be the unit of this analysis. There are various ways to summarize albuterol use on this, for example by looking at:

- daily number of inhalations
- albuterol use exceeding 4 inhalations (Yes/No)
- albuterol use exceeding 12 inhalations (Yes/No)

Exploratory analyses using all these patient days can be performed to predict occurrence of CE-COPD event in the next day (for example, using logistic regression). Exploratory predictive analyses will be reported separately.

7.5.2.4. Summary Descriptive Statistics of Initial and Recurrent Clinical COPD Exacerbation Rates

Proportion of patients with at least 1 CE-COPD and proportion of patients with recurrent events will be presented.

7.5.3. Predicting Severe CE-COPD/Moderate CE-COPD from Multiple Device-Use-Measures

Predictive analysis will be performed by the data analytics group. Additional details may be specified in a separate report. Exploratory predictive analyses will be reported separately.

8. SENSITIVITY ANALYSIS

There will be no sensitivity analysis performed in this study.

9. MULTIPLE COMPARISONS AND MULTIPLICITY

No adjustment for multiplicity will be applied.

10. SAFETY ANALYSIS

10.1. General

The ITT analysis set will be used for all safety analyses.

10.2. Duration of Exposure to ABS eMDPI

Duration of exposure to ABS eMDPI (days and weeks) for the individual patient is the number of days the patient took at least 1 inhalation from the ABS eMDPI. Patients receive the ABS eMDPI devices at Baseline and subsequently by courier on Day 21. Duration of exposure is determined from all eMDPIs used by a patient and it is the total number of unique dates recorded by the eMDPIs from the dispense date and return date of a given device, inclusive. Note, if a patient uses more than 1 eMDPI device on a given day, it is still only 1 day of exposure for that given day. The patient's last date of contact or study completion date will be used as the device return date if the device return date is missing.

Duration of exposure (days and weeks) will be summarized using descriptive statistics overall, and by CE-COPD status and by CE-COPD severity.

Exposure to IMP, expressed in mcg units, will also be summarized using descriptive statistics. Average daily exposure, average weekly exposure, and the maximum exposure in a single day will be summarized overall, and by CE-COPD status and CE-COPD severity. One inhalation recorded by the ABS eMDPI is equivalent to 90 mcg.

10.3. Time on Study

Duration of time on study (days and weeks) will be summarized using descriptive statistics overall, and by CE-COPD status and by CE-COPD severity.

10.4. Adverse Events

All treatment emergent adverse events will be coded using the MedDRA (Medical Dictionary for Regulatory Activities). Adverse events will be included as treatment emergent based on the date of the baseline (ie, the earliest date an ABS eMDPI device was dispensed). Each patient will be counted only once in each PT or SOC category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility [Table 5 in Section 7.1.4 of the protocol], defined as related or with missing relationship; overall and by severity), serious adverse events, CE-COPD related adverse events, and adverse events leading to withdrawal from the study, COPD exacerbations by severity, and COPD exacerbations by deterioration.

Patient listings for all adverse events, serious adverse events, and adverse events leading to withdrawal will be presented.

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the CSR.

Any adverse event or serious adverse event with a missing start date will be considered treatment emergent.

10.5. Deaths

A listing of deaths by patient and narratives will be provided, if any patient dies during the study.

10.6. Clinical Laboratory Tests

Any patient who experiences menarche following screening will be required to have a negative urine pregnancy test prior to dosing with IMP. If a patient has a positive urine pregnancy test, then she will be discontinued from the study. A urine pregnancy test for women of childbearing potential will be performed at the Screening and Final/Early Termination visit.

A listing of urine pregnancy test by patient will be provided.

10.7. Physical Examinations

Physical examinations will be performed at the Screening, exacerbation visits, and Final/Early Termination visit.

A physical examination that includes, at a minimum, skin, lungs, cardiovascular, respiratory, gastrointestinal, and neurological assessments are completed at the Screening visit (eg, baseline values), exacerbation visits, and Final/Early Termination visit. Height (to be obtained at the Screening visit only) and weight will also be measured and recorded. Any pre-existing abnormality will be reported as a part of medical history and any ongoing abnormality identified at screening and any new findings or clinically significant change (worsening) identified at an exacerbation visit or the Final/Early Termination visit will be reported as an adverse event.

10.8. Concomitant Medications or Therapies

Concomitant therapies and medications, including medications that are taken on an as needed basis and occasional therapies, will be monitored during the study. Details of prohibited medications may be found in Section 5.6 of the study protocol. All concomitant medications will be coded using the WHO Drug Dictionary.

The incidence of concomitant therapies and medications will be summarized using descriptive statistics by therapeutic class category and PT term. Patients are counted only once in each therapeutic class, and only once in each PT category. Concomitant therapies and medications for a given patient will include all medications up to the end of the patient's participation in the study (date of completion, withdrawal, lost to follow-up, or death).

A listing of all concomitant therapies and medications by patient and the study day the therapy or medication was started will be provided.

11. TOLERABILITY VARIABLES AND ANALYSIS

Tolerability was not specifically defined for this study.

12. PHARMACOKINETIC ANALYSIS

Not applicable.

13. PHARMACODYNAMIC ANALYSIS

Not applicable.

14. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

Not applicable.

15. BIOMARKER ANALYSIS

Not applicable.

16. IMMUNOGENICITY ANALYSIS

Not applicable.

17. ANCILLARY STUDIES ANALYSIS

Not applicable.

18. PLANNED INTERIM ANALYSIS

Not applicable.

19. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS[®] version 9.1.3 or higher.

20. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

20.1. Intent-To-Treat Analysis Set

Statistical Analysis Plan Section	Protocol Section	Protocol Description	Statistical Analysis Plan Change	Rationale
3.1	9.2.1	The intent-to-treat (ITT) analysis set will include all enrolled patients regardless of whether or not a patient took any IMP. A patient is considered enrolled according to the status reported in the database. This analysis population will be used for summarization of patient disposition.	The intent-to-treat (ITT) analysis set will include all enrolled patients regardless of whether a patient took any investigational medicinal product (IMP). A patient is considered enrolled according to the status reported in the database. This analysis set will be used for endpoint analysis and safety analysis.	Patient disposition will be summarized using all patients entered into the database not just enrolled patients, since all patients are needed to descriptively summarize patients screened, patients screened but not enrolled and reason for non-enrollment. All endpoint and safety analyses will use the ITT analysis set.

20.2. Modified Intent-To-Treat Analysis Set

Statistical Analysis Plan Section	Protocol Section	Protocol Description	Statistical Analysis Plan Change	Rationale
3.2	9.2.2	The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set that will include only the patients who used the IMP at any time during the study. This analysis population will be used for endpoint analysis”.	The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set that will include patients who used the IMP at any time during the study and patients who did not use the IMP at any time during the study provided these patients complied with study requirements and the ABS eMDPI inhalers were available for data download at the end of the study.	This study is to evaluate the relationship between as-needed usage of ABS eMDPI and CE-COPD/severe CE-COPD. As-needed usage may include no usage if patients’ health did not require ABS eMDPI use. Endpoint analyses will be summarized using the ITT analysis set.

20.3. Safety Analysis Set

Statistical Analysis Plan Section	Protocol Section	Protocol Description	Statistical Analysis Plan Change	Rationale
3.3	9.2.3	The safety analysis set will include all enrolled patients who receive at least 1 dose of the test IMP. In this analysis population, treatment will be assigned based on the treatment patients actually received unless otherwise specified. This analysis population will be used for analysis and summarization of safety data.	The safety analysis set will include all enrolled patients who receive at least 1 dose of the IMP.	There is only one IMP in this study. The sentence regarding how treatment will be assigned was deleted for clarity. Safety analyses will be summarized using the ITT analysis set.

20.4. Predicting Severe CE-COPD/Moderate CE-COPD from Multiple Device-Use-Measures

Statistical Analysis Plan Section	Protocol Section	Protocol Description	Statistical Analysis Plan Change	Rationale
7.5.3	9.5.2.1	The multiple device-use-measures will be used as predictors of CE-COPD in stepwise selection logistic regression models to select significant predictors in a forward manner.	Predictive analysis will be performed by the data analytics group. Additional details may be specified in a separate report. Exploratory predictive analyses will be reported separately.	Clarification. Analysis was removed from the SAP as this analysis will be performed separately by the data analytics group.

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