Clinical Study Protocol with Amendment 02

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 (18 Years of Age or Older) with Asthma

Study Number ABS-AS-30064

NCT02969408

Protocol with Amendment 02 Approval Date: 22 February 2017

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(Phase 3B)

IND Number: 104532; NDA Number: N/A; BLA Number: N/A; EudraCT Number: N/A

EMA Decision Number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

Protocol Approval Date: 26 July 2016

Protocol with Amendment 01 Approval Date: 08 September 2016

Protocol with Amendment 02 Approval Date: 22 February 2017

Sponsor

Teva Branded Pharmaceutical
Products R&D, Inc.
41 Moores Road
Frazer, Pennsylvania 19355
United States of America

Information regarding clinical laboratories and other departments and institutions is found in Appendix A.

Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

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AMENDMENT HISTORY

The protocol for study ABS-AS-30064 (original protocol dated 26 July 2016)

Amendment 01	08 September 2016 no patients enrolled to date
Amendment 02	22 February 2017 3 patients enrolled to date

The Summary of Changes to the Protocol includes corresponding reason/justification for each change and is provided in Section 16.

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02

Original Protocol Dated 26 July 2016

IND Number: 104532; NDA Number: N/A; BLA Number: N/A; EudraCT Number: N/A

EMA Decision Number of Pediatric Investigation Plan: Not applicable

Article 45 or 46 of 1901/2006 does not apply

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 (18 Years of Age or Older) with Asthma

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, investigational medicinal products (IMP) shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations.

Principal Investigator	**Signature**	**Date**

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]	[redacted]	22 Feb 2017

CLINICAL STUDY PROTOCOL SYNOPSIS

Study ABS-AS-30064

Title of Study: 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 (18 Years of Age or Older) with Asthma

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Investigational New Drug (IND) Number: 104532; **New Drug Application (NDA) Number:** Not applicable; **Biological License Application (BLA) Number:** Not applicable; **EudraCT Number:** Not applicable

EMA Decision Number of Pediatric Investigation Plan: Not applicable; **Article 45 or 46 of 1901/2006 does not apply**.

Name of Test Investigational Medicinal Product (IMP): Albuterol sulfate (ABS) multidose dry powder inhaler with an eModule (eMDPI)

EudraVigilance (EV) code for the IMP, if applicable: Not applicable

Type of the Study: Phase 3B

Indication: Exacerbation-prone asthma

Is This Study Conducted to Investigate the New Use of an Approved, Marketed Product? No

Number of Investigational Centers Planned: Approximately 45

Countries Planned: United States

Planned Study Period: Approximately 9 months

Number of Patients Planned (Total): Approximately 500 patients will be screened to achieve approximately 400 enrolled patients. A subset of patients (n=100) who agree to participate at specific sites will wear an accelerometer on the wrist to measure sleep disruption index (SDI). A second subset of patients (n=100) who agree to participate at specific sites will wear an accelerometer on the ankle to measure total daily steps (TDS).

Study Population: The cohort will consist of patients 18 years of age or older with exacerbation-prone asthma, defined as at least 1 documented "severe" clinical asthma exacerbation (CAE; defined in Section 6.1.1 of the protocol) in the past 12 months, currently on moderate- to high-dose inhaled corticosteroid (ICS) with or without a long-acting beta agonist (LABA) and with uncontrolled asthma quantified as an Asthma Control Questionnaire-5 (ACQ-5) score ≥1.5.

Objectives and Endpoints

The objectives of this study are to explore the pattern and amount of albuterol use (as captured in the ABS eMDPI), alone or in combination with other study data, preceding a CAE and in particular, a severe CAE (as diagnosed by the investigators per the protocol). The hypothesis is that albuterol use will increase several days prior to a severe CAE and can serve as a marker of asthma deterioration.

The endpoints of the trial are the primary outcome measure (ie, CAE/severe CAE) and the primary outcome predictor (ie, albuterol use) alone or in combination with secondary predictors (ie, other study data). Multiple correlates of CAE/severe CAE focused on albuterol use, alone or in combination with other study data, will be modeled to determine which patterns best predict the subsequent development of CAE/severe CAE.

For albuterol use, parameters of interest will include (1) the total number of inhalations in the days preceding the peak of a severe CAE, (2) the number of days prior to the peak of a severe CAE when albuterol use increased, (3) the number of albuterol uses in the 24 hours preceding a severe CAE. 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), SDI, 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 moderate CAE or severe CAE. Inspiratory flow values are obtained from the eMDPI, SDI is obtained for a subset of patients who agree to participate at specific sites (n=100) from an accelerometer worn on the wrist, and TDS is obtained for a subset of patients who agree to participate at specific sites (n=100) from an accelerometer worn on the ankle. Baseline disease state and demographic information will be obtained at screening.

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

The safety endpoints for this study include the following:

- adverse event data
- physical examinations

General Design: This is a 12-week, multicenter, open-label study to evaluate the relationship between as-needed usage of ABS eMDPI and CAE/severe CAE in adult patients at least 18 years of age with exacerbation-prone asthma. 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 2-week screening period 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, and review asthma 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 short-acting beta$_2$ agonists (SABA), short-acting muscarinic antagonists (SAMA), or SABA/SAMA combination, into storage. Patients may continue the use of other asthma and non-asthma medications as advised by their physician without changes unless a change is 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 asthma 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 and subsequently by courier on Day 21. Patients will be instructed to return all inhalers to the site at the last study visit or early termination. At the last study visit or early termination, patients will be queried for adverse events, concomitant medications, and asthma 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 sites and to 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).

Brief Summary of Study Design for the Trial Registry:

This is a 12-week, multicenter, open-label study to evaluate the relationship between ABS eMDPI and CAE in adult patients at least 18 years of age with exacerbation-prone asthma. The ABS eMDPI dose will be 90 mcg, 1 to 2 inhalations every 4 hours as needed, but patient dosing will not be limited to this dosing regimen. The purpose of this study is to evaluate the relationship between albuterol dosing and CAE.

Method of Randomization and Blinding: This is an open-label study and there will be no blinding.

Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate

Test IMP: The ABS eMDPI dose will be 90 mcg, 1 to 2 inhalations every 4 hours as needed.

Reference IMP: Not applicable

Placebo IMP: Not applicable

Duration of Patient Participation and Maximal Exposure to IMP: The total duration of patient participation in the study is planned to be 14 weeks (2 weeks screening period and 12 weeks intervention period).

Study Duration: Approximately 9 months

End of Study: End of study is defined as the last visit of the last patient.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: No treatment is planned by the sponsor after the end of the study. Patients should be treated with standard of care after withdrawal from or termination of the study, as appropriate.

Inclusion Criteria: Patients may be enrolled in the study only if they meet all of the following criteria:

a. The patient is male or female, 18 years of age or older, with a physician diagnosis of asthma.

b. The patient has had at least 1 episode of a severe CAE (as described in Section 6.1.1 of the protocol) over the past 12 months before screening. If on a biologic (eg, omalizumab, mepolizumab, or reslizumab) and/or post-bronchial thermoplasty, exacerbation has occurred after these interventions.

c. The patient's ACQ-5 score at the time of screening is ≥1.5.

d. The patient is using a moderate-dose ICS, equivalent to at least 440 mcg daily of fluticasone propionate) (see Table 1).

Table 1: Moderate-Dose Inhaled Corticosteroid Treatment Equivalent to at Least 440 mcg Daily of Fluticasone Propionate

ICS Treatment	Total Daily Dose (mcg) Equivalent to at Least 440 mcg Daily of Fluticasone Propionate
Beclomethasone dipropionate	≥ 320 mcg
Budesonide	≥ 720 mcg
Flunisolide	≥ 640 mcg
Mometasone	≥ 400 mcg
Ciclesonide	≥ 320 mcg
Fluticasone furoate	≥ 100 mcg

ICS=inhaled corticosteroid

e. All asthma controller treatments are at a stable dose for 3 months prior to the screening visit.

f. The patient's baseline asthma therapy regimen, including oral corticosteroids, leukotriene antagonists, 5-lipoxygenase inhibitors, LABA, long-acting muscarinic agent, or cromolyn, biologicals, theophylline, or mepolizumab, is allowed.

g. The patient must be able to demonstrate appropriate use of albuterol from the ABS eMDPI.

h. The patient is able to provide written informed consent.

i. The patient must be willing and able to comply with study requirements as specified in the protocol, including the use of a wearable accelerometer for the subset of patients who consent to use of the device.

j. The patient is willing to discontinue all other rescue or maintenance SABA or anti-muscarinic agents and replace them with the study-provided ABS eMDPI for the duration of the trial.

k. Women of childbearing potential (not surgically sterile or ≥2 years postmenopausal) must have exclusively same-sex partners or use a highly effective method of birth control and must agree to continue the use of this method for the duration of the study and for 30 days after discontinuation of the IMP. Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (ie, <1% per year) when used consistently and correctly. Highly effective methods of birth control in this study include combined (estrogen- and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, and sexual abstinence.

Exclusion Criteria: Patients will not be enrolled in this study if they meet any of the following criteria:

a. The patient has any clinically significant medical condition (treated or untreated) that, in the opinion of the investigator, would interfere with participation in the study.

b. The patient has any other confounding underlying lung disorder other than asthma.

c. The patient has used an investigational drug within 5 half-lives of it being discontinued, or 1 month of visit 2, whichever is longer.

d. The patient is a pregnant or lactating woman, or plans to become pregnant during the study. Note: Any woman becoming pregnant during the study will be withdrawn from the study.

e. The patient is either an employee or an immediate relative of an employee of the investigational center.

f. The patient is known to be allergic to albuterol or any of the excipients in the IMP or rescue medication formulation (ie, lactose). Dietary lactose intolerance does not exclude the patient from inclusion in the study or as per the investigator's medical discretion.

g. The patient has a history of drug or alcohol abuse within 2 years prior to the screening visit.

h. The patient has a history or presence of "silent" infections, including positive testing for human immunodeficiency virus types 1 and 2, hepatitis B, hepatitis C, and tuberculosis. Note: A history of a positive tuberculosis skin test without active tuberculosis may be acceptable only if the patient has received an accepted prophylactic treatment regimen and has no clinical evidence of active disease. Patients with a history of hepatitis C who have undergone treatment and achieved a sustained virologic response may be eligible if they meet all other selection criteria and receive medical monitor approval.

i. A member of the patient's household is participating in the study at the same time.

Statistical Considerations:

Sample Size Rationale: Assuming an expected dropout rate of 10%, it is recommended that 400 patients be enrolled so that 360 evaluable patients complete the study. This rationale is based on a review of relevant literature, as follows.

Based on previous studies of a poorly-controlled, exacerbating asthma cohort, it is expected that between 20% and 25% of patients at risk in this patient population will experience a CAE (event) over 3 months, resulting in 72 to 90 expected CAE events in this study. In addition, it is expected that approximately 6.7% and 15% of subjects at risk in this patient population will experience moderate and severe events, respectively, resulting in approximately 78 events (24 moderate events and 54 severe events) in the study.

This sample size (n=400 patients; 72 to 90 CAE events) is considered adequate for fulfillment of the study objectives using univariate and multivariate analyses to evaluate the relationship of the pattern of albuterol use, inspiratory flow, SDI, and TDS data associated with the subsequent development of a moderate CAE or severe CAE. Per the study by Patel et al 2013b, a statistically significant relationship was established between prior mean daily SABA usage at baseline and subsequent CAE, studying 45 exacerbations ($p<0.006$).

In the present study, approximately 72 to 90 CAE events are desired for this trial because the model's fitting of the current study involves the analysis of multiple predictors as described in more detail below.

Risk models published in the literature have typically included between 4 and 6 covariates/risk factors 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, CAE), 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. The rule of thumb when building logistic regression models is 1 predictor variable for every 10 events. Therefore, this sample size would be adequate for predicting the primary outcome (CAE) 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 CAE in the model for this patient population.

Analysis of Endpoints: The multiple device-use-measures will be used as predictors of CAE in the following stepwise selection logistic regression models to select significant predictors in a forward manner:

1. albuterol usage
2. albuterol usage + inspiratory flow values
3. albuterol usage + SDI
4. albuterol usage + TDS
5. albuterol usage + inspiratory flow values + SDI
6. albuterol usage + inspiratory flow values + TDS

Demographic variables collected at study enrollment will also be considered as predictors. Because the device-use-measures will be collected continuously over time, these measures could be used to derive many potential predictors of risk. For example, with respect to albuterol use, a patient using the inhaler 3 times in the span of a 2-day or 3-day period could be a strong predictor of a CAE, but a better marker for risk might be 10 times in the span of a week. There are no prior robust data to inform these decisions; 1 possible benefit of this work will be to examine the relationship between multiple functional forms for the device-use-measures to determine which forms have predictive power.

Furthermore, the effect of including interaction terms in the model (ie, testing the assumption of additivity of predictors on the log odds scale) will also be studied. The primary hypothesis under consideration is that >12 inhalations of SABA dosing will have higher odds of CAE risk relative to 0 to 12 inhalations per day. This dosing scheme is consistent with the approved labelling for albuterol inhalation products. Pair-wise interactions will be assessed at the 0.01 significance level to avoid weak interaction signals that would potentially not translate when applying the risk score to new cohorts. Goodness-of-fit tests may be applied to make sure that the finally selected model fits the data closely. The C-statistic, as described by Hosmer et al, will be used to compare the goodness of fit of various logistic regression models in terms of how well the predictor(s) discriminate between patients with and without CAE.

Efficacy Analysis: Efficacy will not be assessed in this study.

Sensitivity Analysis: Sensitivity will not be assessed in this study.

Multiple Comparisons and Multiplicity: Not applicable

Analysis of Tertiary/Exploratory/Other Endpoints: Not applicable

Safety Analyses: Safety data will be collected over the 12-week intervention period and will be descriptively summarized using appropriate summary statistics for the safety analysis set.

Tolerability Analysis: Tolerability is not specifically defined.

Pharmacokinetic Analysis: Not applicable

Pharmacodynamic Analysis: Not applicable

Pharmacokinetic/Pharmacodynamic Analysis: Not applicable

Biomarker Analysis: Not applicable

Immunogenicity Analysis: Not applicable

Ancillary Studies Analysis: Not applicable

Planned Interim Analysis: Not applicable

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LIST OF ABBREVIATIONS

Abbreviation	Term
ABS	albuterol sulfate
ACQ-5	Asthma Control Questionnaire-5
CAE	clinical asthma exacerbation
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
EIB	exercise-induced bronchospasm
eMDPI	multidose dry powder inhaler with an eModule
EV	EudraVigilance
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GPSP	Global Patient Safety and Pharmacovigilance
HFA	hydrofluoroalkane
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intent-to-treat
LABA	long-acting beta agonist
LSO	local safety officer
MDI	metered dose inhaler
MDPI	multidose dry powder inhaler
MIF	maximal inhalational flow

Abbreviation	Term
mITT	modified intent-to-treat
OCS	oral corticosteroid
PEF	peak expiratory flow
RSI	reference safety information
SABA	short-acting $beta_2$ agonist
SAMA	short-acting muscarinic antagonist
SDI	sleep disruption index
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TDS	total daily steps
ULN	upper limit of normal
USA	United States of America

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

Asthma is one of the most common chronic diseases (NAEPP 1997). This condition affects the airway passages of the lungs and is characterized by airway inflammation and bronchial hyper-responsiveness (MMWR Surveillance Summaries 2002, NAEPP 1997). During acute asthmatic episodes, the airway passages become narrower and more obstructed, resulting in coughing, wheezing, tightness of the chest, shortness of breath, and increased mucus production (NAEPP 1997, US Dept of HHS 1998). It is believed that these asthma symptoms may be associated with chronic changes in airway structure and function, increasing the morbidity and mortality of those affected (MMWR Surveillance Summaries 2002).

As the recommended drug for relief of acute asthmatic symptoms and as the prophylaxis for exercise-induced bronchoconstriction, short-acting beta$_2$ agonists (SABA), such as albuterol, are a mainstay of asthma management. The use of inhaled aerosol medications for asthma is ideal because inhalation delivers relatively low doses of the drug rapidly to the site of action. This preferred administration mode achieves high drug concentrations in the airways while minimizing systemic side effects (Dolovich et al 2005). Inhaled albuterol aerosols are the most commonly prescribed treatments for the relief of bronchoconstriction. PROAIR® (albuterol sulfate [ABS]) RESPICLICK Inhalation Aerosol is available in the United States of America and delivers the equivalent of 90 mcg of albuterol base ex-mouthpiece per actuation. More detailed prescribing information for this product may be found in the Investigator's Brochure (IB).

Although albuterol has traditionally been administered via conventional "press-and-breathe" metered dose inhalers (MDIs), inefficient inhaler technique (ie, inability to properly coordinate actuation with inspiration) is a common problem with these devices; as a consequence, delivery of the active drug to the airways can be compromised, potentially resulting in suboptimal clinical benefits (Allen et al 2003, Kamps et al 2000, Larsen et al 1994, Molimard et al 2003). To eliminate the necessity for coordinating actuation with inspiration, Teva has developed the breath-actuated inhaler PROAIR® RESPICLICK, which utilizes a formulation blend of ABS with lactose as an excipient. Breath actuation has been found to reduce administration errors in comparison with conventional MDIs (Lenney et al 2000, Price et al 1999). ABS is a beta$_2$-adrenergic agonist with the chemical name α1 [(tert butylamino) methyl]-4-hydroxy-m-xylene-α,α′-diol sulfate (2:1) [salt]. PROAIR® RESPICLICK delivers the equivalent of 90 mcg of albuterol base ex-mouthpiece per actuation and has been approved in the USA since March of 2015.

In this study, 90 mcg of ABS is delivered via a multidose dry powder inhaler (MDPI) with an eModule (eMDPI) sitting on the upper part of the device for the purposes of detecting and storing usage information. A more detailed description of the product is given in Section 5.1.1. The eMDPI stores information on the date, time, and inspiratory flow values each time a patient takes a dose. In addition, a subset of patients who agree to participate at specific sites will wear an accelerometer on the wrist as a marker of sleep disruption, and a second subset of patients who agree to participate at specific sites will wear an accelerometer on the ankle to quantify daily physical activity. Information from eMDPI and wearable devices will be used to determine

if they can help predict the subsequent development of a clinical asthma exacerbation (CAE) or severe CAE.

1.2. Findings from Nonclinical and Clinical Studies

In the clinical development program for PROAIR® RESPICLICK, the investigational medicinal product (IMP) was reported using nomenclature other than that of the then-unbranded product. Within this document, we update the name of the IMP to the marketed product, PROAIR® RESPICLICK, to promote alignment with current medical practice.

Brief summaries of nonclinical pharmacology, pharmacokinetics, toxicology, and clinical studies are provided in the following sections. More detailed information is provided in the IB and the package insert for PROAIR® RESPICLICK.

1.2.1. Nonclinical Studies

In a 2-year study in Sprague-Dawley rats, ABS caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 15 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In another study, this effect was blocked by the co-administration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, ABS showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 210 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). ABS was not mutagenic in the Ames test or a mutation test in yeast. ABS was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay. Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 310 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Pre-clinical intravenous studies in rats with ABS have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain. Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

1.2.2. Clinical Studies

Bronchospasm Associated with Asthma: In two 12-week, randomized, double-blind, placebo-controlled studies of identical design (Study 1 and Study 2), PROAIR® RESPICLICK was compared to a matched placebo dry powder inhaler in 153 and 163 asthmatic patients, respectively, 12 to 76 years of age, at a dose of 180 mcg albuterol 4 times daily. Patients were maintained on inhaled corticosteroid (ICS) treatment. Serial measurements of forced expiratory volume in 1 second (FEV_1) demonstrated that 2 inhalations of PROAIR® RESPICLICK produced significantly greater improvement in FEV_1 area under the plasma concentration-time curve from time 0 to 6 hours after IMP administration over the pre-treatment value than placebo in Study 1. Results of Study 2 were consistent with those of Study 1. In a double-blind, randomized, placebo-controlled, single-dose, crossover study evaluating PROAIR®

RESPICLICK and PROAIR® HFA in 71 adult and adolescent patients 12 years of age and older with persistent asthma, PROAIR® RESPICLICK had bronchodilator efficacy that was significantly greater than placebo at administered doses of 90 and 180 mcg.

Exercise-Induced Bronchospasm: In a randomized, single-dose, crossover study in 38 adult and adolescent patients with exercise-induced bronchospasm (EIB), 2 inhalations of PROAIR® RESPICLICK taken 30 minutes before exercise prevented EIB for the hour following exercise (defined as the maintenance of FEV_1 within 80% of postdose, pre-exercise baseline values) in 97% (37 of 38) of patients as compared to 42% (16 of 38) of patients who received placebo. Patients who participated in these clinical studies were allowed to use concomitant steroid therapy.

More detailed information is provided in the IB and the package insert for PROAIR® RESPICLICK.

1.2.2.1. Clinical Safety and Efficacy Studies

A total of 1120 patients were treated with PROAIR® RESPICLICK during the clinical development program. The most common adverse reactions (≥1% and >placebo) were back pain, pain, gastroenteritis viral, sinus headache, and urinary tract infection. In a long-term study of 168 patients treated with PROAIR® RESPICLICK for up to 52 weeks (including a 12-week, double-blind period), the most commonly reported adverse events (≥5%) were upper respiratory infection, nasopharyngitis, sinusitis, bronchitis, cough, oropharyngeal pain, headache, and pyrexia. In a small cumulative-dose study, tremor, palpitations, and headache were the most frequently occurring (≥5%) adverse events.

More detailed information is provided in the IB and the package insert for PROAIR® RESPICLICK.

1.3. Known and Potential Benefits and Risks to Patients

1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product

This open-label study is being undertaken to determine if a specific pattern of changes in ABS eMDPI use can predict a patient's risk for subsequent development of a moderate CAE or severe CAE event. In addition to ABS eMDPI use, inhalation flow values and sleep disruption index (SDI) and total daily steps (TDS) data will be used to determine if changes in these measures can further improve the prediction of risk for severe CAE.

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. Furthermore, the instructions for the use of ABS eMDPI are identical to that of the currently approved PROAIR® RESPICLICK. Therefore, it is unlikely that the inclusion of the eModule will add additional risk to the approved product. Information on the risks of PROAIR® RESPICLICK can be found in

the package insert. Additional information regarding benefits and risks of ABS eMDPI to patients may be found in the IB.

In summary, the benefit and risk assessment for ABS eMDPI is favorable following review of the outlined data.

1.3.2. Overall Benefit and Risk Assessment for This Study

This is an open-label study in patients 18 years of age or older with exacerbation-prone asthma being conducted for assessment of relationship of the use of ABS eMDPI and other electronically collected data with a severe CAE event. The study data will be used to inform patients, providers, and the design of future intervention trials to demonstrate improved clinical outcomes. It is anticipated that risks to patients beyond those listed in the PROAIR® RESPICLICK label are unlikely.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives and Endpoints

The study objectives and endpoints are as follows:

Objective	Endpoints
The **objectives** of this study are to explore the pattern and amount of albuterol use (as captured in the ABS eMDPI), alone or in combination with other study data, preceding a CAE and in particular, a severe CAE (as diagnosed by the investigators per the protocol). The hypothesis is that albuterol use will increase several days prior to a severe CAE and can serve as a marker of asthma deterioration.	The endpoints of the trial are the primary outcome measure (ie, CAE/severe CAE) and the primary outcome predictor (ie, albuterol use) alone or in combination with secondary predictors (ie, other study data). Multiple correlates of CAE/severe CAE focused on albuterol use, alone or in combination with other study data, will be modeled to determine which patterns best predict the subsequent development of CAE/severe CAE. For albuterol use, parameters of interest will include (1) the total number of inhalations in the days preceding the peak of a severe CAE, (2) the number of days prior to the peak of a severe CAE when albuterol use increased, (3) the number of albuterol uses in the 24 hours preceding a severe CAE. 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), SDI, 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 moderate CAE or severe CAE. Inspiratory flow values are obtained from the eMDPI, SDI is obtained for a subset of patients who agree to participate at specific sites (n=100) from an accelerometer worn on the wrist, and TDS is obtained for a subset of patients who agree to participate at specific sites (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 asthma.	The safety endpoints for this study include the following: • adverse event data • physical examinations

2.1.1. Justification of the Endpoints

The endpoints of the trial are the primary outcome measure (ie, CAE/severe CAE) and the primary outcome predictor (ie, albuterol use) alone or in combination with secondary predictors (ie, other study data). Multiple correlates of CAE focused on albuterol use, alone or in combination with other study data, will be modeled to determine which patterns best predict the subsequent development of CAE/severe CAE.

The increased use of SABA, deterioration in peak expiratory flow, and worsening of symptoms are associated with CAE in previously reported studies (Tattersfield et al 1999, Patel et al 2013b).

In the present trial, SABA use will be monitored electronically concomitant with the CAE event. Inspiratory flow values will be used as a surrogate for peak expiratory flow, because the study data require no additional patient effort and are also digital and concurrent. SDI is an effortless, digital concomitant correlate of sleep disruption, a key asthma symptom complex. Furthermore, TDS is an effortless, digital concomitant correlate of dyspnea on exertion, which is also a key symptom of asthma deterioration. These parameters therefore are likely to help predict the subsequent development of a moderate CAE or severe CAE.

3. STUDY DESIGN

3.1. General Design

This is a 12-week, multicenter, open-label study to evaluate the relationship between as-needed usage of ABS eMDPI and CAE/severe CAE in adult patients at least 18 years of age with exacerbation-prone asthma. 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 2-week screening period 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, and review asthma 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 (SAMA), or SABA/SAMA combination into storage. Patients may continue use of other asthma and non-asthma 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 asthma 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 and subsequently by courier on Day 21. Patients will be instructed to return all inhalers to the site at the last study visit or early termination. At the last study visit or early termination, patients will be queried for adverse events, concomitant medications, and asthma 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 sites 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.

3.2. Planned Number of Patients and Countries

Approximately 500 patients will be screened to achieve 400 enrolled patients. A subset of patients (n=100) who agree to participate at specific sites will wear an accelerometer on the wrist to measure SDI. A second subset of patients (n=100) who agree to participate at specific sites will wear an accelerometer on the ankle to measure TDS.

The number of evaluable patients is planned to be 360. Details on the definition of evaluable patients and sample size are given in Section 9.

The study is planned to be conducted in the United States in approximately 45 investigational centers.

3.3. Justification for Study Design and Selection of Population

The current study is designed to capture the natural history of CAE and to assess the relationship of exacerbation events with data that are readily obtainable using ABS eMDPI in a routine clinical setting. Thus, there is no control group, and intervention is kept to a minimum (ie, only an eModule in surveillance mode and a wearable accelerometer are added to routine care).

Prior work has documented a relationship between SABA usage rates and the subsequent occurrence of CAE. The relationship between (1) 3 different metrics of baseline albuterol use over 2 weeks of monitoring with an electronic module and (2) future severe CAE was explored in a nested cohort study (Patel et al 2013b). The study was undertaken in real-world asthma patients (16 to 65 years of age) at risk of severe asthma exacerbations, receiving budesonide/formoterol twice a day as maintenance therapy for 24 weeks, with albuterol as-needed for relief of symptoms. The nested cohort comprised 147 patients out of a total number of 303 patients for the parent trial (Patel et al 2013a). Severe CAE was defined as either the use of systemic corticosteroids for at least 3 days or a hospitalization or emergency visit due to asthma that required the use of systemic corticosteroids. Exacerbations were quantified over the 24-week observation period.

Average daily albuterol use (quantified over the 2-week monitoring period at the baseline of the study) was the metric that performed best as a predictor of risk of future severe CAE. The 45 participants in the group with subsequent severe asthma (exacerbation group) had 1 exacerbation each using 5.5±9.7 actuations per day of albuterol, compared to 1.83±3.3 actuations per day in the non-exacerbating group (102 patients). For average daily albuterol use, univariate logistic regression for the risk of a future severe asthma exacerbation showed that higher baseline mean daily albuterol use was a significant predictor of severe asthma exacerbations (odds ratio=1.24 [95% confidence interval, 1.06-1.46]; $p<0.006$).

In a less recent study, change in peak expiratory flow (PEF), symptoms, and use of rescue SABA were quantified during the 425 severe CAE events that occurred during a 12-month parallel group study (FACET) in which low and high doses of budesonide with and without formoterol were compared in patients with asthma (Tattersfield et al 1999). Oral corticosteroids (OCS) were prescribed for severe CAE, the main study endpoint, defined as the need for a course of OCS (n=311) or a reduction in morning PEF of >30% on 2 consecutive days. PEF, symptoms, and bronchodilator use over the 14 days before and after the CAE were obtained from diary cards.

CAEs were characterized by a gradual fall in PEF over several days, followed by more rapid changes over 2 to 3 days. An increase in symptoms and rescue SABA use occurred in parallel, and both the severity and time course of the changes were similar in all treatment groups. CAE identified by the need for OCS were associated with more symptoms and smaller changes in PEF than those identified on the basis of PEF criteria. Female sex was the main patient characteristic associated with an increased risk of having a severe CAE. CAE were characterized predominantly by a change in symptoms or a change in PEF, but the pattern was not affected by the dose of ICS or by formoterol use. Thus, in the study of Tattersfield et al, multiple physiologic changes preceeded CAE. These changes were noted as early as 10 days before a CAE event, and were well-established 5 days before a CAE event. These results suggest that patients who develop severe CAEs will have a predictable change in their clinical course that could be used to identify patients at risk for a severe event. In the current study, information from the eMDPI and accelerometer will be used to determine if changes in these measures can predict the development of severe CAE. If appropriate predictors of risk can be determined, patients at risk for severe morbidity and possibly mortality could be identified and receive interventions that could change the subsequent clinical outcomes.

3.4. Stopping Rules for the Study

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed as they are reported from the investigational centers to identify safety concerns (Section 7.1.5).

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event of:

- new toxicological or pharmacological findings or safety issues invalidating the earlier positive benefit-risk assessment
- discontinuation of the development of the investigational medicinal product (IMP)
- the number of severe CAEs collected.

If the whole study will be stopped, the patients that are terminated early will be followed according to Withdrawal Criteria and Procedures for the Patient (Section 4.3).

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 1. Detailed descriptions of each procedure and assessment are provided in Section 6 (endpoint assessments) and Section 7 (safety assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 1: Study Procedures and Assessments

Study period	**Pre-intervention**		**Intervention**			
Visit number	**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 to14 days** After CAE 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	
Vital signs measurement[c]	X					
Urine pregnancy test for women of childbearing potential	X					X
Complete ACQ-5	X					
Inform patients of study compliance for eMDPI and accelerometer, and requirement for provider visit in the event of CAE	X	X	X	X		
Assess for asthma 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 of all asthma 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 consent to participate at specific sites 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 ABS eMDPI devices at visit 2 and subsequently by courier on Day 21. Patients will be instructed to return all inhalers to the site at the last study visit or early termination. 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; CAE=clinical asthma exacerbation; SDI=sleep disruption index; TDS=total daily steps; eMDPI=multidose dry powder inhaler with an eModule; IMP=investigational medicinal product; V=visit.
Screening and baseline visits may be combined.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be enrolled are not granted by Teva (Appendix C).

4.1. Patient Inclusion Criteria

Patients may be enrolled in this study only if they meet all of the following criteria:

a. The patient is male or female, 18 years of age or older, with a physician diagnosis of asthma.

b. The patient has had at least 1 episode of severe CAE as described in Section 6.1.1 over the past 12 months before screening. If on a biologic (eg, omalizumab, mepolizumab, or reslizumab) and/or post-bronchial thermoplasty, exacerbation has occurred after these interventions.

c. The patient's Asthma Control Questionnaire-5 (ACQ-5) score at the time of screening is ≥1.5 (Juniper et al 2005).

d. The patient is using a moderate-dose ICS, equivalent to at least 440 mcg daily of fluticasone propionate (see Table 2).

Table 2: Moderate-Dose Inhaled Corticosteroid Treatment Equivalent to at Least 440 mcg Daily of Fluticasone Propionate

ICS Treatment	Total Daily Dose (mcg) Equivalent to at Least 440 mcg Daily of Fluticasone Propionate
Beclomethasone dipropionate	≥ 320 mcg
Budesonide	≥ 720 mcg
Flunisolide	≥ 640 mcg
Mometasone	≥ 400 mcg
Ciclesonide	≥ 320 mcg
Fluticasone furoate	≥ 100 mcg

ICS=inhaled corticosteroid

e. All asthma controller treatments are at a stable dose for 3 months prior to the screening visit.

f. The patient's baseline asthma therapy regimen, including oral corticosteroids, leukotriene antagonists, 5-lipoxygenase inhibitors, LABA, long-acting muscarinic agent, or cromolyn, biologicals, theophylline, or mepolizumab, is allowed.

g. The patient must be able to demonstrate appropriate use of albuterol from the ABS eMDPI.

h. The patient is able to provide written informed consent.

i. The patient must be willing and able to comply with study requirements as specified in the protocol, including the use of a wearable accelerometer for the subset of patients who consent to use of the device.

j. The patient is willing to discontinue all other rescue or maintenance SABA or anti-muscarinic agents and replace them with the study-provided ABS eMDPI for the duration of the trial.

k. Women of childbearing potential (not surgically sterile or ≥2 years postmenopausal) must have exclusively same-sex partners or use a highly effective method of birth control and must agree to continue the use of this method for the duration of the study and for 30 days after discontinuation of the IMP. Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (ie, <1% per year) when used consistently and correctly. Highly effective methods of birth control in this study include combined (estrogen- and progestogen-containing) or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, and sexual abstinence. Additional details can be found in Appendix E.

4.2. Patient Exclusion Criteria

Patients will not be enrolled in this study if they meet any of the following criteria:

a. The patient has any clinically significant medical condition (treated or untreated) that, in the opinion of the investigator, would interfere with participation in the study.

b. The patient has any other confounding underlying lung disorder other than asthma.

c. The patient has used an investigational drug within 5 half-lives of it being discontinued, or 1 month of visit 2, whichever is longer.

d. The patient is a pregnant or lactating woman or plans to become pregnant during the study. Note: Any woman becoming pregnant during the study will be withdrawn from the study.

e. The patient is either an employee or an immediate relative of an employee of the investigational center.

f. The patient is known to be allergic to albuterol or any of the excipients in the IMP or rescue medication formulation (ie, lactose). Dietary lactose intolerance does not exclude the patient from inclusion in the study or as per the investigator's medical discretion.

g. The patient has a history of drug or alcohol abuse within 2 years prior to the screening visit.

h. The patient has a history or presence of "silent" infections, including positive testing for human immunodeficiency virus types 1 and 2, hepatitis B, hepatitis C, and tuberculosis. Note: A history of a positive tuberculosis skin test without active tuberculosis may be acceptable only if the patient has received an accepted

prophylactic treatment regimen and has no clinical evidence of active disease. Patients with a history of hepatitis C who have undergone treatment and achieved a sustained virologic response may be eligible if they meet all other selection criteria and receive medical monitor approval.

i. A member of the patient's household is participating in the study at the same time.

4.3. Withdrawal Criteria and Procedures for the Patient

Each patient is free to withdraw from the study at any time, without prejudice to their continued care. Patients must be withdrawn from the study if any of the following events occur:

a. Patient withdraws consent or requests discontinuation from the study for any reason.

b. Patient develops an illness that would interfere with his/her continued participation.

c. Patient is noncompliant with the study procedures and assessments or administration of ABS eMDPI, in the opinion of the investigator.

d. Patient takes prohibited concomitant medications as defined in this protocol.

e. A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.

f. The sponsor requests withdrawal of the patient.

g. Patient experiences an adverse event or other medical condition that indicates to the investigator that continued participation is not in the best interest of the patient.

Patients should be treated with standard of care after withdrawal from or termination of the study, as appropriate.

Investigators should attempt to obtain information on patients in the case of withdrawal or discontinuation. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal or discontinuation.

See Appendix F for information regarding how the study will define and address patients who are lost to follow-up to help limit the amount and impact of missing data.

If the reason for withdrawal is an adverse event, monitoring will be continued as applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a healthcare professional, or until a determination of a cause unrelated to the IMP or study procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; both the adverse events page and termination page of the CRF will be completed at that time.

All assessments should be performed according to the protocol for the final visit or upon early termination (visit 5) if possible. Patients are required to return the ABS eMDPI (used and unused) upon withdrawal from the study.

4.4. Replacement of Patients

A patient who is enrolled but does not complete the 12-week intervention period will not be replaced.

4.5. Rescreening

A patient who is screened but not enrolled (eg, because inclusion and exclusion criteria were not met or enrollment did not occur within the specified time) may be considered for screening again if, eg, there is a change in the patient's medical background or a modification of study inclusion and exclusion criteria.

If the patient is rescreened, an informed consent form (ICF) will need to be resigned.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. Minimal information includes, but is not limited to, demography, screening failure details, eligibility criteria, and any serious adverse events.

5. TREATMENTS

5.1. Investigational Medicinal Products Used in the Study

Patients will receive initial ABS eMDPI devices at visit 2 and subsequently by courier on Day 21. Patients will be instructed on the proper use of the device, including the requirement for use within 60 seconds of opening the cap. Patients will be instructed to return all inhalers to the site at the last study visit or early termination (visit 5). Compliance to ABS eMDPI administration will be monitored.

5.1.1. 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."

The plastic inhaler comprises a reservoir containing inhalation powder, a metering system, a mouthpiece with dust cover, and an eModule sitting on top of the drug delivery compartment. 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, predefined events such as cap opening and inhalation.

Additional details may be found in Table 3 and in the IB.

5.1.1.1. 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.

5.1.1.2. Dose Modification and Dose Stratification

Not applicable.

5.1.2. Reference Investigational Medicinal Product

Not applicable.

5.1.3. Placebo Investigational Medicinal Product

Not applicable.

Table 3: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP	Reference IMP
Trade name	ABS eMDPI	Not applicable	Not applicable
Formulation	Inhalation powder	Not applicable	Not applicable
Unit dose strength	90 mcg	Not applicable	Not applicable
Route of administration	Inhalation	Not applicable	Not applicable
Dosing instructions	1 to 2 inhalations every 4 hours as needed	Not applicable	Not applicable
Packaging	IMP will be provided in a box	Not applicable	Not applicable
Manufacturer	Teva Pharmaceutical Industries, Ltd. Jerusalem, Israel	Not applicable	Not applicable

ABS=albuterol sulfate; eMDPI=multidose dry powder inhaler with an eModule; IMP=Investigational Medicinal Product; Ltd=limited.

5.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products

5.2.1. Storage and Security

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all IMPs received, and any discrepancies are reported and resolved before use of the IMP.

The IMP must be stored at monitored room temperature (15°C to 25°C [59°F to 77°F]) and not exposed to extreme heat, cold, or humidity.

5.2.2. Labeling

Supplies of IMP will be labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements.

5.2.3. Accountability

Each IMP shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMPs for initial distribution to patients and other study materials from the sponsor are correctly received, recorded, handled, and safely and properly stored in accordance with the Code of Federal Regulations (CFR) and used in accordance with this protocol. All additional dispensing of the IMP will be by courier direct to the patient as needed.

Only patients enrolled in the study may receive IMP. The investigator (or designee) will instruct the patient to store the IMP according to the instructions on the label, if applicable, or will give instructions in an appropriate form. Patients will be instructed to return all IMP (empty, partially used, and unused inhalers) to the investigational center at the final visit or at early termination.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Patients will return all inhalers at the end of the study to the site for reconciliation.

A record of IMP accountability (ie, IMP and other study materials received, used, retained, and returned) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused inhalers will be disposed of at the end of the study following collection of data from the device and with sponsor's approval.

Further guidance and information may be provided in the Study Reference Manual.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The prescribed dose of ABS eMDPI used in this study (ie, 90 mcg, 1 to 2 inhalations every 4 hours as needed) was selected based on the prescribing information for PROAIR® RESPICLICK, which has the same drug delivery design as ABS eMDPI.

PROAIR® RESPICLICK is indicated for the management of asthma and relief of acute symptoms of asthma in adults and children 4 years and older, and for the prevention of exercise-induced bronchoconstriction. For the relief of acute asthma symptoms, PROAIR® RESPICLICK is recommended at a dosage of 2 inhalations (ie, 180 mcg of albuterol base ex-mouthpiece) repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, 1 inhalation every 4 hours may be sufficient. The recommended dosage for PROAIR® RESPICLICK for the prevention of EIB in adults and children 4 years of age or older is 2 inhalations 15 to 30 minutes before exercise. To date, the overall results of clinical studies provide robust and consistent evidence that PROAIR® RESPICLICK is effective for the treatment or prevention of bronchospasm in adult and adolescent patients with obstructive airway disease.

5.4. Treatment After the End of the Study

No treatment is planned by the sponsor after the end of the study. Patients should be treated with standard of care after withdrawal from or termination of the study, as appropriate.

5.5. Restrictions

There are no additional restrictions beyond the inclusion and exclusion criteria in this study.

5.6. Prior and Concomitant Medication or Therapy

Any prior or concomitant medication a patient has had within 30 days before enrollment and up to the end of study will be recorded on the CRF. Trade name and international nonproprietary

name (if available), indication, dose, and start and end dates of the administered medication will be recorded. The sponsor will encode all medication according to the World Health Organization drug dictionary.

The following medications will be prohibited during this study:

- any immunosuppressive or immunomodulatory agents including, but not limited to, methotrexate, cyclosporine, and interferon-α for 2 months prior to visit 2
- levalbuterol during the 12-week intervention period
- other forms of albuterol MDI during the 12-week intervention period
- any albuterol nebulizer outside of a CAE

At each investigational center visit and during monthly phone calls, the patients will be asked whether they have taken any medications (other than IMP), including over-the-counter medications, vitamins, or herbal or nutritional supplements, since the previous visit.

Concomitant medication and treatment will be recorded through visit 5.

5.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. A check of compliance with IMP intake will be performed during each monthly phone call after the IMP has been dispensed, and IMP accountability records will be completed.

If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study.

Exposure to IMP will be assessed as required.

5.8. Randomization and Blinding

This is an open-label study and there will be no blinding.

5.9. Total Blood Volume

No blood will be collected for study-related assessments.

6. ASSESSMENT OF EFFICACY

Efficacy will not be assessed in this study.

The endpoints of the trial are the primary outcome measure (ie, CAE/severe CAE) and the primary outcome predictor (ie, albuterol use) alone or in combination with secondary predictors (ie, other study data). Multiple correlates of CAE/severe CAE focused on albuterol use, alone or in combination with other study data, will be modeled to determine which patterns best predict the subsequent development of CAE/severe CAE. Albuterol use, inspiratory flow, SDI, TDS, disease state at baseline and demographics at baseline, will be used to evaluate these endpoints.

6.1. Assessments

6.1.1. Clinical Asthma Exacerbation

The diagnosis of CAE will be determined by the investigator using the definitions shown below, which are based on the official American Thoracic Society/European Respiratory Society statement (Reddel et al 2009).

In this study, "CAE" is an occurrence of either "severe CAE" or "moderate CAE."

- Severe CAE is defined as a CAE that involves worsening asthma such that
  - the treating physician elects to administer prednisone (or equivalent glucocorticoid treatment) at least 10 mg prednisone equivalent above baseline (Table 4), for at least 3 days

    AND
  - an unscheduled provider visit such as an office visit, urgent care visit, emergency care visit, or hospitalization
- Moderate CAE is defined as a CAE that involves worsening asthma such that
  - the treating physician elects to administer prednisone (or equivalent glucocorticoid treatment) at least 10 mg prednisone equivalent above baseline (Table 4), for at least 3 days

    OR
  - an unscheduled provider visit such as an office visit, urgent care visit, emergency care visit, or hospitalization associated with an increase in asthma therapy that does not qualify for "severe CAE" as defined above

Table 4: 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®

6.1.2. Albuterol Use

Albuterol usage data will be downloaded using extraction software directly from eMDPI devices collected from the patients at their final study visit after return of the device to the depot.

For albuterol use, parameters of interest will include (1) the total number of inhalations in the days preceding the peak of a severe CAE, (2) the number of days prior to the peak of a severe CAE when albuterol use increased, (3) the number of albuterol uses in the 24 hours preceding a severe CAE.

6.1.3. Inhalational Flow Values Upon Albuterol Dosing

Inhalational flow values will include (1) MIF, (2) inhalational volume, (3) inhalational duration and (4) time to MIF. The inhalational flow data will be downloaded using extraction software directly from eMDPI devices collected from the patients at their final study visit after return of the device to the depot.

6.1.4. Accelerometry

From a subset of patients who agree to participate at specific sites, SDI and TDS data will be downloaded using extraction software directly from the wearable accelerometer devices collected from the patients at their final study visit or transmitted to the central data center via Wi-Fi on a daily basis. A description of the analysis is provided in the Statistical Analysis Plan.

The wearable Philips accelerometer falls into a product classification that the Food and Drug Administration (FDA) has deemed 510(k) exempt.

See the User Guide for a description of care and use of wearable devices.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events and physical examinations.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to the test IMP. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication1
- drug interactions

All CAE events require documentation by the Investigator in the CAE Exacerbation Page in the CRF. All evaluations entered into the CAE Exacerbation Page require an in-person visit (Vz "Exacerbation Visit", see Table 1). This visit can co-incide with an unscheduled provider visit (Section 6.1.1) or can be scheduled separately if an unscheduled provider visit has not occurred. Investigational centers must obtain source documentation of all asthma exacerbations that occur during the treatment period to confirm the accuracy of the information obtained from the patient.

7.1.2. Recording and Reporting of Adverse Events

For recording of adverse event, the study period is defined for each patient as the time period from signature of the ICF to the end of visit 5 (Table 1). The period for reporting treatment-emergent adverse events is defined as the period after the 1st dose of IMP is administered and until end of visit 5.

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the test IMP. For serious adverse events, the serious adverse event form must be completed, and the serious adverse event must be reported immediately (Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events after the defined period.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe.” All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a healthcare professional; or until a determination of a cause unrelated to the test IMP or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded both on the source documentation and the CRF.

The relationship of each adverse event to test IMP and study procedures and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Further details are given in the Safety Monitoring Plan.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as one of the following:

- **Mild:** No limitation of usual activities
- **Moderate:** Some limitation of usual activities
- **Severe:** Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Test Investigational Medicinal Product

The relationship of an adverse event to the test IMP is characterized as follows:

Table 5: The Relationship of an Adverse Event to the Test IMP

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death
- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study.

- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **all** of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- alanine aminotransferase or aspartate aminotransferase increase of >3x the upper limit of normal (ULN)
- total bilirubin increase of >2x ULN
- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase)

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI of the ABS eMDPI in this study is the IB.

A serious adverse event that is not included in the Listing of Adverse Reactions in the IB by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

The sponsor's Global Patient Safety and Pharmacovigilance (GPSP) will determine the expectedness for all serious adverse events.

For the purpose of suspected unexpected serious adverse reaction (SUSAR) reporting, the version of the IB at the time of occurrence of the SUSAR applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the test IMP, must be reported to the

sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (a contract research organization [CRO] in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's GPSP.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the test IMP (no reasonable possibility, reasonable possibility)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death
  - cause of death (whether or not the death was related to IMP)
  - autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the test IMP, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences form/Extensible Markup Language file to the LSO/CRO for submission to the competent authorities, Independent Ethics Committee/Institutional Review Board (IEC/IRBs), and investigators, according to regulations. The investigator must ensure that the IEC/IRB is also informed of the event in accordance with national and local regulations.

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the test IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of ABS eMDPI and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to ABS eMDPI

7.1.6. Protocol-Defined Adverse Events not for Expedited Reporting

For purposes of this protocol, there are no anticipated or previously recognized serious adverse events or reactions to be reported to competent authorities in an expedited procedure.

7.1.7. Protocol-Defined Adverse Events of Special Interest

No protocol-defined adverse events of special interest were identified for this study.

7.1.8. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Pregnancy

Any female patient becoming pregnant during the study will discontinue the test IMP.

All pregnancies of women participating in the study that occur during the study, within at least 5 half-lives after the end of study are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3).

The investigator is not required to report patients who are found to be pregnant between screening and baseline, provided no protocol-related procedures were applied.

All female patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or voluntary abortion). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy in the woman participating in the study does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.3. Medication Error and Special Situations Related to the Investigational Medicinal Products

Any administration of IMP that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria specified in the protocol (Appendix C), or as a deviation, in the patients source documents, regardless of whether or not an adverse event occurs as a result. When meeting protocol violation criteria, all instances of incorrect IMP administration should be categorized on the CRF as “Non-Compliance to investigational medicinal product (IMP).”

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of

IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.

3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to an IMP, as a result of one's professional or non-professional occupation.
7. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.

7.4. 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 they will be discontinued from the study. Procedures for reporting pregnancy are provided in Section 7.1.5.3.

7.5. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit only) and weight, will be performed at the time points detailed in Table 1.

A physical examination will include, at a minimum, skin, lungs, cardiovascular, respiratory, gastrointestinal, and neurological assessments. Height (to be obtained at the screening visit only) and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.6. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, and heart rate) will be measured at the screening visit (Table 1) for inclusion criteria assessment only and will not be used for safety assessment.

7.7. Electrocardiography

Electrocardiogram will not be measured in this study.

8. ASSESSMENT OF PHARMACOKINETICS / PHARMACODYNAMICS / BIOMARKERS / PHARMACOGENOMICS / IMMUNOGENICITY / ANCILLARY STUDIES

Pharmacokinetic, pharmacodynamic, biomarker, pharmacogenomics, immunogenicity, or other ancillary parameters will not be evaluated in this study.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed and justified in the clinical study report (CSR).

9.1. 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. The rationale is based on a review of the relevant literature, as follows.

Based on previous studies of a poorly-controlled, exacerbating asthma cohort (Bateman et al 2015, Ko et al 2012, McCarren et al 1998, Quezada et al 2016), it is expected that between 20% and 25% of subjects at risk in this patient population will experience a CAE (event) over 3 months resulting in 72 to 90 expected CAE events in this study. In addition, it is expected that approximately 6.7% and 15% (Bousquet et al 2007, Ko et al 2012, Kuna et al 2007, and Rabe et al 2006) of subjects at risk in this patient population will experience moderate and severe events, respectively, resulting in approximately 78 events (24 moderate events and 54 severe events) in this study.

This sample size (n=400 patients; 72 to 90 CAE events) is considered adequate for fulfillment of the study objectives using univariate and multivariate analyses to evaluate the relationship of the pattern of albuterol use, inspiratory flow, SDI, and TDS data associated with the subsequent development of a moderate CAE or severe CAE. Per the study by Patel (Patel et al 2013b), a statistically significant relationship was established between prior mean daily SABA usage at baseline and subsequent CAE, studying 45 exacerbations ($p<0.006$).

In the present study, approximately 72 to 90 CAE events are desired for this trial because the model's fitting of the current study involves the analysis of multiple predictors as described in more detail below.

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, CAE), 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 (Peduzzi et al 1996, Harrell et al 1984, Laupacis et al 1997). 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 (CAE) 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 CAE in the model for this patient population.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

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.

9.2.2. 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 only the patients who used the IMP at any time during the study. This analysis population will be used for endpoint analysis.

9.2.3. Safety Analysis Set

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.

9.3. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses, that is, there is no plan to estimate (impute) missing data, unless otherwise specified in the analysis plan. Detailed data imputation rules will be described in the statistical analysis plan, if applicable.

9.3.1. Handling Withdrawals and Missing Data

Missing data will not be imputed, unless otherwise specified.

9.4. Study Population

The cohort will consist of patients 18 years of age or older with exacerbation-prone asthma, defined as at least 1 documented “severe” CAE; (Section 6.1.1) in the past 12 months, currently on medium- to high-dose ICS with or without LABA and with uncontrolled asthma quantified as an ACQ-5 score ≥1.5).

9.4.1. Patient Disposition

Data from patients screened; patients screened but not enrolled and reason for non enrollment; patients who are enrolled; patients enrolled but not treated; patients in the ITT, safety, and mITT analysis sets; 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, %).

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history and prior medications and therapies, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and

maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary. This will be based on the ITT analysis population.

9.5. Endpoint Analysis

9.5.1. Endpoints

The endpoints of the trial are the primary outcome measure (CAE) and the primary predictor (ie, albuterol use) alone or in combination with secondary predictors (ie, other study data) of CAE. Several parameters of CAE focused on albuterol use, alone or in combination with other study data (inspiratory flow, SDI, TDS, disease state at baseline, and demographics at baseline), will be modeled to determine which patterns best predict the subsequent development of CAE/severe CAE. For albuterol use, examples of correlates of CAE of interest include (1) the total number of inhalations in the days preceding the peak of a severe CAE, (2) the number of days prior to the peak of a severe CAE when albuterol use increased, (3) the number of albuterol uses in the 24◦hours preceding a severe CAE. Therefore, endpoints are not designated as either primary or secondary.

Albuterol use and inspiratory flow values are obtained from the eMDPI, SDI is obtained for a subset of patients (n=100) from an accelerometer worn on the wrist, and TDS is obtained for a subset of patients (n=100) from an accelerometer worn on the ankle. Baseline disease state and demographic information will be obtained at screening.

The following 8 surrogate measures of sleep disruption are available from the accelerometer worn on the wrist; (i) sleeptime average total time in bed, (ii) sleeptime average total sleep time, (iii) sleeptime average sleep latency time, (iv) sleeptime average wakening after sleep onset, (v) total time awake at night, (vi) longest sleeptime wake episode, (vii) daytime average minutes asleep, and (viii) longest daytime sleep episode.

The SDI for analysis in this study is the composite endpoint derived from the summation of sleeptime average sleep latency time, longest sleeptime wake episode, and total time awake at night. These 3 surrogate measures were correlated significantly with SABA rescue use (sleeptime average sleep latency time (r=0.78), longest sleeptime wake episode (r=0.73), and total time awake at night (r=0.65) (Krouse et al 2008).

9.5.2. Planned Method of Analysis

The mITT analysis set (Section 9.2.2) will be used for all endpoint analyses. Individual listings will be presented by patient.

9.5.2.1. Endpoint Analysis

The multiple device-use-measures will be used as predictors of CAE in the following stepwise selection logistic regression models to select significant predictors in a forward manner:

1. albuterol usage
2. albuterol usage + inspiratory flow values
3. albuterol usage + SDI

4. albuterol usage + TDS
5. albuterol usage + inspiratory flow values + SDI
6. albuterol usage + inspiratory flow values + TDS

Demographic variables and disease state information collected at study enrollment will also be considered as predictors. Because the device-use-measures will be collected continuously over time, these measures could be used to derive many potential predictors of risk. For example, with respect to albuterol use, a subject using the inhaler 3 times in the span of a 2-day or 3-day period could be a strong predictor of a CAE, but a better marker for risk might be 10 times in the span of a week. There are no prior robust data to inform these decisions; 1 possible benefit of this work will be to examine the relationship between multiple functional forms for the device-use-measures to determine which forms have predictive power.

Furthermore, the effect of including interaction terms in the model (ie, testing the assumption of additivity of predictors on the log odds scale) will also be studied. The primary hypothesis under consideration is that >12 inhalations of SABA dosing will have higher odds of CAE risk relative to 0 to 12 inhalations per day. This dosing scheme is consistent with the approved labelling for albuterol inhalation products. Pair-wise interactions will be assessed at the 0.01 significance level to avoid weak interaction signals that would potentially not translate when applying the risk score to new cohorts. Goodness-of-fit tests may be applied to make sure that the finally selected model fits the data closely. The C-statistic will be used to compare the goodness of fit of various logistic regression models in terms of how well the predictor(s) discriminate between patients with and without CAE (Hosmer et al 2013).

9.5.2.2. Sensitivity Analysis

There will be no sensitivity analysis performed in this study.

9.6. Multiple Comparisons and Multiplicity

Since the goal of this analysis is to build a risk prediction model, no adjustment for multiplicity will be applied.

9.7. Safety Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.3).

Safety assessments and time points are provided in Table 1.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or System Organ Class 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 [Section 7.1.4], defined as related or with missing relationship; overall and by severity), serious adverse events, and adverse events leading to withdrawal from the study. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics.

For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (physical examination) based on predefined criteria will be provided as well.

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.

9.8. Tolerability Analysis

Tolerability was not specifically defined.

9.9. Planned Interim Analysis

There will be no formal interim analysis performed in this study.

9.10. Reporting Deviations from the Statistical Analysis Plan

Deviations from the statistical analysis plan, along with the reasons for the deviations, will be described in protocol amendments, the statistical analysis plan, the CSR, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Refer to Appendix C for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations and violations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

Details are given in the Study Reference Manual.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 CFR [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with competent authorities.

See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IECand IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix G for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

Investigational centers must obtain source documentation of all asthma exacerbations that occur during the treatment period to confirm the accuracy of the information obtained from the patient at monthly phone calls during the 12-week intervention period.

13. FINANCING AND INSURANCE

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the IMP is delivered.

Patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are inter alia, damages to health, and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete FDA 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

14. PUBLICATION POLICY

See Appendix I for information regarding the publication policy.

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 02 Dated 22 February 2017

The primary reason for this amendment is a re-evaluation of the sample size needed to meet the study endpoints. This amendment is considered to be substantial (ie, it requires approval by Competent Authority, IEC, and/or IRB) by the Sponsor. All text that was removed is denoted by a strikethrough and all added text is underlined. Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Clinical Study Protocol Synopsis (Other section affected by this change: Section 3.2)		
Number of Investigational Centers Planned: Approximately ~~50~~ 45	**Number of Investigational Centers Planned:** Approximately 45	The word "Approximately" added to match text in the body of the protocol and reduced to 45 sites
Clinical Study Protocol Synopsis (Other sections affected by this change: Section 3.2 and Section 9.1)		
Number of Patients Planned (Total): Approximately ~~6~~500 patients will be screened to achieve approximately ~~5~~400 enrolled patients.	**Number of Patients Planned (Total):** Approximately 500 patients will be screened to achieve approximately 400 enrolled patients.	Re-evaluation of sample size to meet study endpoints
Clinical Study Protocol Synopsis (Other section affected by this change: Section 9.4)		
Study Population: The cohort will consist of patients 18 years of age or older with exacerbation-prone asthma, defined as at least 1 documented "severe" clinical asthma exacerbation (CAE; defined in Section 6.1.1 of the protocol) in the past 12 months, currently on moderate- to high-dose inhaled corticosteroid (ICS) with or without a long-acting beta agonist (LABA) and with uncontrolled asthma quantified as an Asthma Control Questionnaire-5 (ACQ-5) score ≥1.5.	**Study Population:** The cohort will consist of patients 18 years of age or older with exacerbation-prone asthma, defined as at least 1 documented "severe" clinical asthma exacerbation (CAE; defined in Section 6.1.1 of the protocol) in the past 12 months, currently on moderate- to high-dose inhaled corticosteroid (ICS) with or without a long-acting beta agonist (LABA) and with uncontrolled asthma quantified as an Asthma Control Questionnaire-5 (ACQ-5) score ≥1.5.	Asthma Control Questionnaire-5 (ACQ-5) added to quantify uncontrolled asthma.

Original text with changes shown	New wording	Reason/Justification for change
Clinical Study Protocol Synopsis (Other section affected by this change: Section 3.1)		
Those meeting entry criteria will be trained on the use of the eMDPI device and, upon demonstrated competency, will receive ~~3~~ ABS eMDPI devices for use as rescue bronchodilators during the study.	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.	Number of devices removed from the sentence to allow for change in the number of devices, if necessary.
Clinical Study Protocol Synopsis (Other sections affected by this change: Section 3.1, Table 1 V4 and footnote e, Section 5.1, and Appendix B, Section 2,b)		
Patients will receive initial eMDPI devices at visit 2 and subsequently by courier on Day~~s~~ 21 ~~and 56~~.	Patients will receive initial eMDPI devices at visit 2 and subsequently by courier on Day 21.	The change was made to reduce the number of Direct to Patient shipments from 2 shipments to 1 shipment.
Clinical Study Protocol Synopsis (Other section affected by this change: Section 4.1)		
Inclusion Criteria b. The patient has had at least 1 episode of severe CAE as described in Section 6.1.1 over the past 12 months before screening. If on a biologic (eg, omalizumab, mepolizumab, or reslizumab) and/or post-bronchial thermoplasty, exacerbation has occurred after these interventions. c. The patient's Asthma Control Questionnaire-5 (ACQ-5) score at the time of screening is ≥1.5. (Juniper et al 2005) .~~must be able to demonstrate appropriate use of albuterol from the ABS eMDPI.~~ d. The patient ~~must be abe to demonstrate appropriate use of albuterol from the ABS eMDPI~~ is using ~~at least~~ a moderate-dose ICS, ~~(~~equivalent to at least 440 mcg daily of fluticasone propionate~~)~~ (see Table 1). ~~and any additional asthma controller at a stable dose for 3 months prior to the screening visit.~~ e. ~~and any additional~~ All asthma controller treatments	**Inclusion Criteria** b. The patient has had at least 1 episode of severe CAE as described in Section 6.1.1 over the past 12 months before screening. If on a biologic (eg, omalizumab, mepolizumab, or reslizumab) and/or post-bronchial thermoplasty, exacerbation has occurred after these interventions. c. The patient's Asthma Control Questionnaire-5 (ACQ-5) score at the time of screening is ≥1.5 (Juniper et al 2005). d. The patient is using a moderate-dose ICS, equivalent to at least 440 mcg daily of fluticasone propionate (Table 1). e. All asthma controller treatments are at a stable dose for 3 months prior to the screening visit. **Moderate-Dose Inhaled Corticosteroid Treatment Equivalent to at Least 440 mcg Daily of Fluticasone Propionate**	Inclusion criteria "b" modified to include instructions for a patient on a biologic and/or post-bronchial thermoplasty. ACQ-5 inclusion criteria added as inclusion criteria" c" with reference in body of protocol. Old inclusion criteria "c" moved to inclusion criteria "f". Inclusion criteria "d" revised and split into "d" and "e" and table added to clarify equivalent doses of moderate-dose ICS to at least 440 mcg daily of fluticasone propionate.

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/Justification for change</th></tr>
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<td>are at a stable dose for 3 months prior to the screening visit.

<u>Moderate-Dose Inhaled Corticosteroid Treatment Equivalent to at Least 440 mcg Daily of Fluticasone Propionate</u>
f. <u>The patient must be able to demonstrate appropriate</u>
<table>
<tr><th>ICS Treatment</th><th>Total Daily Dose (mcg) Equivalent to at Least 440 mcg Daily of Fluticasone Propionate</th></tr>
<tr><td>Beclomethasone dipropionate</td><td>≥ 320 mcg</td></tr>
<tr><td>Budesonide</td><td>≥ 720 mcg</td></tr>
<tr><td>Flunisolide</td><td>≥ 640 mcg</td></tr>
<tr><td>Mometasone</td><td>≥ 400 mcg</td></tr>
<tr><td>Ciclesonide</td><td>≥ 320 mcg</td></tr>
<tr><td>Fluticasone furoate</td><td>≥ 100 mcg</td></tr>
</table>
ICS=inhaled corticosteroid
<u>use of albuterol from the ABS eMDPI.</u>
</td>
<td>f. The patient must be able to demonstrate appropriate
<table>
<tr><th>ICS Treatment</th><th>Total Daily Dose (mcg) Equivalent to at Least 440 mcg Daily of Fluticasone Propionate</th></tr>
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<tr><td>Ciclesonide</td><td>≥ 320 mcg</td></tr>
<tr><td>Fluticasone furoate</td><td>≥ 100 mcg</td></tr>
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ICS=inhaled corticosteroid
use of albuterol from the ABS eMDPI.
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Original text with changes shown	New wording	Reason/Justification for change
Clinical Study Protocol Synopsis (Other section affected by this change: Section 4.2)		
Exclusion Criteria c. The patient has used an investigational drug within 5 half-lives of it being discontinued, or 1 month of visit 2, whichever is longer. f. The patient is known to be allergic to albuterol or any of the excipients in the IMP or rescue medication formulation (ie, lactose). Dietary lactose intolerance does not exclude the patient from inclusion in the study or as per the investigator's medical discretion.	**Exclusion Criteria** c. The patient has used an investigational drug within 5 half-lives of it being discontinued, or 1 month of visit 2, whichever is longer. f. The patient is known to be allergic to albuterol or any of the excipients in the IMP or rescue medication formulation (ie, lactose). Dietary lactose intolerance does not exclude the patient from inclusion in the study or as per the investigator's medical discretion.	Visit 2 added to exclusion criteria "c" for clarity. Revised exclusion criteria "f" to include allergy to excipients of the IMP or rescue medication formulation.
Clinical Study Protocol Synopsis (Other sections affected by this change: Section 3.2 and Section 9.1)		
Sample Size Rationale: Assuming an expected dropout rate of 10%, it is recommended that ~~5~~400 patients be enrolled so that 43~~5~~60 evaluable patients complete the study. Based on previous studies of a poorly-controlled, exacerbating asthma cohort, it is expected that between 20% and 25% of patients at risk in this patient population will experience a CAE (event) over 3 months, resulting in ~~90~~72 to ~~113~~90 expected CAE events in this study. In addition, it is expected that approximately 6.7% and 15% of subjects at risk in this patient population will experience moderate and severe events, respectively, resulting in approximately 78 events (24 moderate events and 54 severe events) in the study. This sample size (n=4~~5~~00 patients; ~~90~~72 to ~~113~~90 CAE events) is considered adequate for fulfillment of the study objectives using univariate and multivariate	**Sample Size Rationale:** Assuming an expected dropout rate of 10%, it is recommended that 400 patients be enrolled so that 360 evaluable patients complete the study. Based on previous studies of a poorly-controlled, exacerbating asthma cohort, it is expected that between 20% and 25% of patients at risk in this patient population will experience a CAE (event) over 3 months, resulting in 72 to 90 expected CAE events in this study. In addition, it is expected that approximately 6.7% and 15% of subjects at risk in this patient population will experience moderate and severe events, respectively, resulting in approximately 78 events (24 moderate events and 54 severe events) in the study. This sample size (n=400 patients; 72 to 90 CAE events) is considered adequate for fulfillment of the study objectives using univariate and multivariate analyses to evaluate the relationship of the pattern of albuterol use,	Re-evaluation of sample size to meet study endpoints

Original text with changes shown	New wording	Reason/Justification for change
analyses to evaluate the relationship of the pattern of albuterol use, inspiratory flow, SDI, and TDS data associated with the subsequent development of a moderate CAE or severe CAE. Per the study by Patel et al 2013b, a statistically significant relationship was established between prior mean daily SABA usage at baseline and subsequent CAE, studying 45 exacerbations (p<0.006). In the present study, approximately ~~90~~72 to ~~113~~90 CAE events are desired for this trial because the model's fitting of the current study involves the analysis of multiple predictors as described in more detail below.	inspiratory flow, SDI, and TDS data associated with the subsequent development of a moderate CAE or severe CAE. Per the study by Patel et al 2013b, a statistically significant relationship was established between prior mean daily SABA usage at baseline and subsequent CAE, studying 45 exacerbations (p<0.006). In the present study, approximately 72 to 90 CAE events are desired for this trial because the model's fitting of the current study involves the analysis of multiple predictors as described in more detail below.	
List of Abbreviations		
ACQ-5 Asthma Control Questionnaire-5	ACQ-5 Asthma Control Questionnaire-5	ACQ-5 added to List of Abbreviations
Section 3.5, Table 1 Study Procedures and Assessments (Other section affected by this change: Appendix B, Study Procedures and Assessments by Visit, Section 1,2, and 3)		
Visit number V1 Day and allowed time windows Day -14 to Day ~~0~~1 Visit number V2 Day and allowed time windows ~~±7 days~~ Visit number Vz Day and allowed time windows ~~±~~Up to 14 days After CAE Start Date Complete ACQ-5 X in Screening column	Visit number V1 Day and allowed time windows Day -14 to Day 1 Visit number V2 Day and allowed time windows Visit number Vz Day and allowed time windows Up to 14 days After CAE Start Date Complete ACQ-5 X in Screening column	Day and allowed time windows corrected for accuracy. Complete ACQ-5 added to Screening visit in Appendix B, Section 1 Sentence added to Appendix B, Section 3, for clarity
Section 6.1.1 Clinical Asthma Exacerbation		
Table 4: Systemic Glucocorticoid Treatment Equivalent to 10 mg of Prednisone	Table 4: Systemic Glucocorticoid Treatment Equivalent to 10 mg of Prednisone	Added Table 4 to clarify systemic glucocorticoid treatment equivalent to 10 mg of prednisone.

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<tr><th><u>Glucocorticoid Treatment</u></th><th><u>Dose (mg) Equivalent to 10 mg of Prednisone</u></th><th><u>Comment</u></th></tr>
<tr><td><u>Cortisone</u></td><td><u>50</u></td><td><u>Includes parenteral</u></td></tr>
<tr><td><u>Hydrocortisone</u></td><td><u>40</u></td><td><u>Cortisol</u></td></tr>
<tr><td><u>Prednisolone</u></td><td><u>10</u></td><td><u>-</u></td></tr>
<tr><td><u>Methylprednisolone</u></td><td><u>8</u></td><td><u>Medrol: includes parenteral SOLU-MEDROL®</u></td></tr>
<tr><td><u>Triamcinolone</u></td><td><u>8</u></td><td><u>-</u></td></tr>
<tr><td><u>Betamethasone</u></td><td><u>0.4</u></td><td><u>-</u></td></tr>
<tr><td><u>Dexamethasone</u></td><td><u>0.4</u></td><td><u>Oral or parenteral DECADRON®</u></td></tr>
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<table>
<tr><th>Glucocorticoid Treatment</th><th>Dose (mg) Equivalent to 10 mg of Prednisone</th><th>Comment</th></tr>
<tr><td>Cortisone</td><td>50</td><td>Includes parenteral</td></tr>
<tr><td>Hydrocortisone</td><td>40</td><td>Cortisol</td></tr>
<tr><td>Prednisolone</td><td>10</td><td>-</td></tr>
<tr><td>Methylprednisolone</td><td>8</td><td>Medrol: includes parenteral SOLU-MEDROL®</td></tr>
<tr><td>Triamcinolone</td><td>8</td><td>-</td></tr>
<tr><td>Betamethasone</td><td>0.4</td><td>-</td></tr>
<tr><td>Dexamethasone</td><td>0.4</td><td>Oral or parenteral DECADRON®</td></tr>
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</td><td></td></tr>
<tr><td colspan="3">Section 6.1.4 Accelerometry</td></tr>
<tr><td>From a subset of patients who agree to participate at specific sites, SDI and TDS data will be downloaded using extraction software directly from the wearable accelerometer devices collected from the patients at their final study visit or transmitted to the central data center via Wi-Fi on a daily basis. <u>A description of the analysis is provided in the Statistical Analysis Plan.</u>

The wearable <u>Philips</u> accelerometer ~~to be used in this study is the Actigraph GT9XLink.This accelerometer has been cleared by~~ <u>falls into a product classification that</u> the Food and Drug Administration (FDA) <u>has</u> deemed 510(k) exempt. ~~through a 50110(k) (K089545)~~</td><td>From a subset of patients who agree to participate at specific sites, SDI and TDS data will be downloaded using extraction software directly from the wearable accelerometer devices collected from the patients at their final study visit or transmitted to the central data center via Wi-Fi on a daily basis. A description of the analysis is provided in the Statistical Analysis Plan.

The wearable Philips accelerometer falls into a product classification that the Food and Drug Administration (FDA) has deemed 510(k) exempt.</td><td>The location of the description of the analysis has been added for completeness.
Teva does not want to include the device model should the device need to be changed for any reason.
Typographical error corrected and update of product classification</td></tr>
</table>

Original text with changes shown	New wording	Reason/Justification for change
~~with the intended use of documenting physical movement associated with physiological monitoring, including sleep.~~ See the ~~Study Reference Manual~~ User Guide for a ~~detailed~~ description of care and use of wearable devices.	See the User Guide for a description of care and use of wearable devices.	
Section 9.5.1 Endpoints		
The following 8 surrogate measures of sleep disruption are available from the accelerometer worn on the wrist; (i) sleeptime average total time in bed, (ii) sleeptime average total sleep time, (iii) sleeptime average sleep latency time, (iv) sleeptime average wakening after sleep onset, (v) total time awake at night, (vi) longest sleeptime wake episode, (vii) daytime average minutes asleep, and (viii) longest daytime sleep episode. The SDI for analysis in this study is the composite endpoint derived from the summation of sleeptime average sleep latency time, longest sleeptime wake episode, and total time awake at night. These 3 surrogate measures were correlated significantly with SABA rescue use (sleeptime average sleep latency time (r=0.78), longest sleeptime wake episode (r=0.73), and total time awake at night (r=0.65) (Krouse et al 2008).	The following 8 surrogate measures of sleep disruption are available from the accelerometer worn on the wrist; (i) sleeptime average total time in bed, (ii) sleeptime average total sleep time, (iii) sleeptime average sleep latency time, (iv) sleeptime average wakening after sleep onset, (v) total time awake at night, (vi) longest sleeptime wake episode, (vii) daytime average minutes asleep, and (viii) longest daytime sleep episode. The SDI for analysis in this study is the composite endpoint derived from the summation of sleeptime average sleep latency time, longest sleeptime wake episode, and total time awake at night. These 3 surrogate measures were correlated significantly with SABA rescue use (sleeptime average sleep latency time (r=0.78), longest sleeptime wake episode (r=0.73), and total time awake at night (r=0.65) (Krouse et al 2008).	SDI endpoints added for clarity.
Section 15 References (Other section affected by this change: Section 9.1)		
Bousquet J, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respiratory Medicine 2007;101:2437-46. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respiratory Medicine (2005) 99, 553-8.	Bousquet J, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respiratory Medicine 2007;101:2437-46. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respiratory Medicine (2005) 99, 553-8.	New references were added to the text and therefore, to the reference list.

Original text with changes shown	New wording	Reason/Justification for change
Krouse HJ, Yarandi H, McIntosh J, Cowen C, Selim V. Assessing sleep quality and daytime wakefulness in asthma using wrist actigraphy, J Asthma 2008;45(5):389-95. Kuna P, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract 2007;61(5):725-36. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006;68:744-53.	Krouse HJ, Yarandi H, McIntosh J, Cowen C, Selim V. Assessing sleep quality and daytime wakefulness in asthma using wrist actigraphy, J Asthma 2008;45(5):389-95. Kuna P, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract 2007;61(5):725-36. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. Lancet 2006;368:744-53.	
Appendix A. Clinical Laboratories and Other Departments and Institutions		
Contract Research Organization ~~PPD~~PRA	**Contract Research Organization** PRA	Change in Contract Research Organization
Appendix B, Study Procedures and Assessments by Visit, Section 2.c, 4th bullet		
• collect wearable accelerometer, if applicable	• collect wearable accelerometer, if applicable	"if applicable" added for clarity

16.2. Amendment 01 Dated 08 September 2016

The primary reason for this amendment is to clarify the definition, collection, and recording of CAEs. This amendment is considered to be substantial (ie, it requires approval by Competent Authority, IEC, and/or IRB) by the Sponsor. All text that was removed is denoted by a strikethrough and all added text is underlined. Table 1 (Study Procedures and Assessments) has been revised to reflect changes described below. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

Changes to the Protocol

Original text with changes shown	New wording	Reason/justification for change
Section 1.1 Introduction (Other sections affected by these changes: Sections 2.1, 3.1, 3.2, 3.5 [Table 1, Footnote d], and 6.1.4)		
In addition, a subset of patients who agree to participate at ~~selected~~ specific sites will wear an accelerometer on the wrist as a marker of ~~nighttime awakening~~ sleep disruption, and a second subset of patients who agree to participate at ~~selected~~ specific sites will wear an accelerometer on the ankle to quantify daily physical activity.	In addition, a subset of patients who agree to participate at specific sites will wear an accelerometer on the wrist as a marker of sleep disruption, and a second subset of patients who agree to participate at specific sites will wear an accelerometer on the ankle to quantify daily physical activity.	This change was made because sites are not selected in a statistical sense but are identified as having agreed to participate in the substudy. Clarification: "nighttime awakening" was changed to "sleep disruption" and "physical" was added to daily activity to better describe these measurements.
Section 2.1 Study Objectives and Endpoints		
The objectives of this study are to ~~determine~~ explore the pattern and amount of albuterol use (as captured in the ABS eMDPI), alone or in combination with other study data,	The objectives of this study are to explore the pattern and amount of albuterol use (as captured in the ABS eMDPI), alone or in combination with other study data,	This change was made because "determine" was not the correct verb.
Section 2.1 Study Objectives and Endpoints (Other sections affected by these changes: Sections 6.1.2 and 9.5.1)		
For albuterol use, parameters of interest will include (1) the total number of inhalations in the days preceding the peak of a severe CAE, (2) the number of days prior to the peak of a severe CAE when albuterol use increased,	For albuterol use, parameters of interest will include (1) the total number of inhalations in the days preceding the peak of a severe CAE, (2) the number of days prior to the peak of a severe CAE when albuterol use increased	This change was made to further define the parameters that will be assessed as endpoints in this study.
Section 2.1 Study Objectives and Endpoints (Other sections affected by these changes: Sections 2.1.1 and 9.1)		
These data will be analyzed using both a univariate and multivariate approach, to determine which patterns best predict the subsequent development of a moderate CAE or severe CAE.	These data will be analyzed using both a univariate and multivariate approach, to determine which patterns best predict the subsequent development of a moderate CAE or severe CAE.	This language was updated to reflect that the data will be used to predict only moderate or severe CAEs and not all CAEs.
Section 3.1 General Design (Other sections affected by this change: Sections 3.5 [Table 1, Footnote e] and 5.1)		
Patients will receive initial eMDPI devices at visit 2 and subsequently ~~in the mail~~ by courier ~~as needed, based on usage pattern~~ on Days 21 and 56.	Patients will receive initial eMDPI devices at visit 2 and subsequently by courier on Days 21 and 56.	Clarification: "in the mail" was changed to "by courier on Days 21 and 56" to indicate they will not be mailed through the US Postal Service on specific days.

Original text with changes shown	New wording	Reason/justification for change
Section 3.1 General Design (Other sections affected by this change: Section 3.5 [Table 1, Footnote e] and 5.1)		
Patients will be instructed to return all inhalers to the site at the last study visit or early termination. At the last study visit, ~~sites must obtain all ABS eMDPI devices~~; patients will be queried for adverse events, concomitant medications, and asthma exacerbations; a physical examination will be completed; and the patient will subsequently be discharged from the trial.	Patients will be instructed to return all inhalers to the site at the last study visit or early termination. At the last study visit, patients will be queried for adverse events, concomitant medications, and asthma exacerbations; a physical examination will be completed; and the patient will subsequently be discharged from the trial.	The text "or early termination. At the last study visit" was added for clarification. The text "sites must obtain all ABS eMDPI devices" was removed as redundant.
Section 3.1 General Design (Other sections affected by this change: Section 3.2)		
The study duration will be approximately 9 months.~~, from the 4th quarter of 2016 through the 3rd quarter of 2017.~~	The study duration will be approximately 9 months.	This change was made to allow flexibility in the start and stop times of the study.
Section 3.1 General Design (Other sections affected by this change: Sections 3.2 and 9.4)		
Two subsets of patients who agree to participate at specific sites and wear an accelerometer either on the ankle to measure ~~daily activity~~ TDS (n=100) or on the wrist to measure ~~sleep quality~~ SDI (n=100) will be instructed on the proper use of these devices at the baseline visit	Two subsets of patients who agree to participate at specific sites 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	The text was moved from Section 9.4 to Section 3.2 and SDI and TDS were used for consistency after defined at first use in Section 1.3.1.
Section 3.3 Justification for Study Design and Selection of Population		
~~Of relevance to current study design,~~ Prior work has documented a relationship between SABA usage rates and the subsequent occurrence of CAE.	Prior work has documented a relationship between SABA usage rates and the subsequent occurrence of CAE.	This change was made because the language was superfluous.
Section 3.5 Study Procedures and Assessments, Table 1 (Other sections affected by these changes: Sections 3.1, 5.1, 5.6, 7.1.2, 12, and Appendix B)		
Day and allowed time windows: **V1: ~~Up to 2 weeks~~ Day -14 to Day 0** **V2: Day 1±7 days ~~1 week~~** **Vz: ±14 days ~~2 weeks~~** **V~~3~~5: Day 84±14 days ~~2 weeks~~**	Day and allowed time windows: **V1: Day -14 to Day 0** **V2: Day 1±7 days** **Vz: ±14 days** **V5: Day 84±14 days**	This change was made to include the days of the study visits. visit 3 was updated to visit 5 because 2 phone visits were added (see below).

Original text with changes shown	New wording	Reason/justification for change
[a] ~~A total of 2 monthly calls will occur between Visit 1 and Visit 3 to collect information about asthma exacerbations and treatments, use of concomitant medications, adverse event information, and to review the instructions for use of ABS eMDPI and the procedure for replacement and return of ABS eMDPI.~~ Investigational centers must obtain source documentation of all asthma exacerbations that occur during the treatment period to confirm the accuracy of the information obtained from the patient.	**V3: Day 28±7 days** **V4: Day 56±7 days** Procedures to be done on these visits as indicated by an X in Table 1: Inform patients of study compliance for eMDPI and accelerometer, and requirement for provider visit in the event of CAE ABS eMDPI dispense, training, collection and accountability Assess for asthma exacerbations Adverse events inquiry Concomitant medication inquiry	These visits were originally included in Footnote a of Table 1 and were moved to the table itself. The footnote was updated to reflect this change and new text was added for clarification.
[e] Patients will receive initial ABS eMDPI devices at visit 2 and subsequently ~~in the mail~~ by courier ~~as needed~~ on Days 21 and 56.	[e] Patients will receive initial ABS eMDPI devices at visit 2 and subsequently by courier on Days 21 and 56.	Footnote e was updated to reflect new information on the delivery of replacement IMP.
Section 4.1 Inclusion Criteria		
Patients may be enrolled in this study only if they meet all of the following criteria: a. The patient is male or female, 18 years of age or older, with a physician diagnosis of ~~uncontrolled~~ asthma. b. The patient has had at least 1 episode of severe CAE ~~(requiring an emergency department visit or hospitalization)~~ as described in Section 6.1.1 over the past 12 months before screening.	Patients may be enrolled in this study only if they meet all of the following criteria: a. The patient is male or female, 18 years of age or older, with a physician diagnosis of asthma. b. The patient has had at least 1 episode of severe CAE as described in Section 6.1.1 over the past 12 months before screening.	Inclusion Criterion a was changed because the original intent was to include the entire asthma population. Inclusion Criterion b was changed to reflect the change made to the definition of CAE.
Section 4.2 Exclusion Criteria		
d. ~~The patient has or has had CAE within 4 weeks of baseline.~~	d. [Criterion deleted]	Exclusion Criterion d was deleted because the risk of CAE is highest in the 30-day period following an exacerbation, and their pattern of albuterol use is of great interest from the research and clinical perspective.

Original text with changes shown	New wording	Reason/justification for change
Section 5.1 Investigational Medicinal Products Used in the Study		
Patients will be instructed on the proper use of the device, including the requirement for use within 60 seconds of opening the cap.	Patients will be instructed on the proper use of the device, including the requirement for use within 60 seconds of opening the cap.	This change was made to specify the need to use the device within 60 seconds of opening the cap or it will time out, and no inhalation data will be collected.
Section 5.1 Investigational Medicinal Products Used in the Study (Table 2 Investigational Medicinal Products Used in the Study)		
Packaging: IMP will be provided in ~~a foil pouch within~~ a box	**Packaging:** IMP will be provided in a box	Language was updated to correct the description of the packaging of IMP
Section 5.2.1 Storage and Security		
The IMP must be stored at monitored room temperature (15ºC to 25ºC [59ºF to 77ºF] and not exposed to extreme heat, cold, or humidity.	The IMP must be stored at monitored room temperature (15ºC to 25ºC [59ºF to 77ºF] and not exposed to extreme heat, cold, or humidity.	Language updated to ensure the investigational centers keep the IMP in monitored conditions.
Section 5.2.3 Accountability		
Patients will be instructed to return all IMP (empty, partially used, and unused inhalers) to the investigational center at the final visit or at early termination. The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Patients will return all inhalers at the end of the study to the site for reconciliation.	Patients will be instructed to return all IMP (empty, partially used, and unused inhalers) to the investigational center at the final visit or at early termination. The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Patients will return all inhalers at the end of the study to the site for reconciliation.	These changes were made to further instruct the investigational centers on the need for patients to return all devices at the end of the study.
Section 6.1 Clinical Asthma Exacerbation (Other sections affected by these changes: Section 7.1.1)		
~~Investigator determined~~ The diagnosis of CAE will be ~~defined~~ determined by the investigator using the definitions shown below, which were adapted from the official American Thoracic Society/European Respiratory Society statement (Reddel et al 2009). ~~This statement defines asthma exacerbation as a worsening of asthma such that the treating physician elected to administer systemic glucocorticoids for at least 3 days, or the patient visited an urgent care clinic or emergency department or~~	The diagnosis of CAE will be determined by the investigator using the definitions shown below, which were adapted from the official American Thoracic Society/European Respiratory Society statement (Reddel et al 2009). In this study, "CAE" is an occurrence of either "severe CAE" or "moderate CAE." • Severe CAE is defined for the purpose of this	The definitions of serious and moderate CAEs were updated to reflect new information. The final statement was moved to Section 7.1.1 because it is the more appropriate section for discussing adverse events.

Original text with changes shown	New wording	Reason/justification for change
~~was hospitalized.~~ In this study, "CAE" is an occurrence of either "severe CAE" or "moderate CAE." ● Severe CAE is defined for the purpose of this study as a CAE that involves worsening asthma ~~respiratory symptoms requiring treament with systemic corticosteroids (with or without antibiotics)~~ such that – the treating physician elects to add prednisone (or equivalent glucocorticoid treatment) at least 10 mg prednisone equivalent above baseline, for at least 3 days AND – an unscheduled provider visit such as, an office visit, urgent care visit, emergency care visit, or hospitalization. ~~Note that a CAE required hospitalization should not be considered an SAE unless it meets other SAE criteria.~~ ● Moderate CAE is defined as a CAE that involves worsening asthma ~~respiratory symptoms requiring treatment with systemic corticosteroids (with or without antibiotics)~~ such that – the treating physician elects to add prednisone (or equivalent glucocorticoid treatment) at least 10 mg prednisone equivalent above baseline, for at least 3 days – OR – an unscheduled provider visit such as, an office visit, urgent care visit, emergency care visit, or hospitalization associated with an increase in asthma therapy that does not qualify for "severe	study as a CAE that involves worsening asthma such that – the treating physician elects to add prednisone (or equivalent glucocorticoid treatment) at least 10 mg prednisone equivalent above baseline, for at least 3 days AND – an unscheduled provider visit such as, an office visit, urgent care visit, emergency care visit, or hospitalization. ● Moderate CAE is defined as a CAE that involves worsening asthma such that – the treating physician elects to add prednisone (or equivalent glucocorticoid treatment) at least 10 mg prednisone equivalent above baselin, for at least 3 days – OR – an unscheduled provider visit such as, an office visit, urgent care visit, emergency care visit, or hospitalization associated with an increase in asthmas therapy that does not qualify for "severe CAE" as defined above.	

Original text with changes shown	New wording	Reason/justification for change
CAE" as defined above. ~~All CAE events will be documented by the investigator in the CAE Exacerbation Page in the CRF. Investigational centers must obtain source documentation of all asthma exacerbations to confirm the accuracy of the information obtained from the patient.~~		
Section 6.1.2 Albuterol Use (Other sections affected by this change: Section 6.1.3)		
Albuterol usage data will be downloaded using extraction software directly from eMDPI devices collected from the patients at their first study visit after return of the device to the depot.	Albuterol usage data will be downloaded using extraction software directly from eMDPI devices collected from the patients at their first study visit after return of the device to the depot.	Language was added for clarification.
Section 6.1.4 Accelerometry		
The wearable accelerometer to be used in this study is the ActiGraph GT9X Link. This accelerometer has been cleared by the (Food and Drug Administration) FDA through a 501(k) (K080545) with the intended use of documenting physical movement associated with physiological monitoring, including sleep.	The wearable accelerometer used in this study is the ActiGraph GT9X Link. This accelerometer has been cleared by the Food and Drug Administration (FDA) through a 501(k) (K080545) with the intended use of documenting physical movement associated with physiological monitoring, including sleep.	This language was added to provide information on the accelerometer used in the study.
Section 7.1.1 Definition of an Adverse Event		
~~Asthma exacerbations will not be considered adverse events unless they are severe enough to require hospitalization of the patient, in which case they will be recorded as serious adverse events.~~ All CAE events require documentation by the Investigator in the CAE Exacerbation Page in the CRF. All evaluations entered into the CAE Exacerbation Page require an in-person visit (Vz "Exacerbation Visit", see Table 1). This visit can co-incide with an unscheduled provider visit (Section 6.1.1) or can be scheduled separately if an unscheduled provider visit has not occurred. Investigational centers must obtain source documentation of all asthma exacerbations that occur during the treatment period to confirm the accuracy of the information obtained from the patient.	All CAE events require documentation by the Investigator in the CAE Exacerbation Page in the CRF. All evaluations entered into the CAE Exacerbation Page require an in-person visit (Vz "Exacerbation Visit", see Table 1). This visit can co-incide with an unscheduled provider visit (Section 6.1.1) or can be scheduled separately if an unscheduled provider visit has not occurred. Investigational centers must obtain source documentation of all asthma exacerbations that occur during the treatment period to confirm the accuracy of the information obtained from the patient.	This change was made because of the requirement for patients to return to the center in the event of an asthma exacerbation and to denote the requirement to record all asthma exacerbations as adverse events.

Original text with changes shown	New wording	Reason/justification for change
Section 7.4 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 ~~at randomization.~~	Any patient who experiences menarche following screening will be required to have a negative urine pregnancy test prior to dosing with IMP.	This change was made to remove the reference to randomization, as this study is open-label.
Section 9.5.2.1 Endpoint Analysis		
7. ~~albuterol usage + SDI + TDS~~ 8. ~~albuterol usage + inspiratory flow values + SDI + TDS~~		Models 7 and 8 cannot be measured as originally proposed because SDI and TDS are subsets of patients. Therefore, the models were deleted.
Furthermore, the effect of including interaction terms in the model (ie, testing the assumption of additivity of predictors on the log odds scale) will also be studied. The primary hypothesis under consideration is that >12 inhalations of SABA dosing will have higher odds of CAE risk relative to 0 to 12 inhalations per day. This dosing scheme is consistent with the approved labelling for albuterol inhalation products. Pair-wise interactions will be assessed at the 0.01 significance level to avoid weak interaction signals that would potentially not translate when applying the risk score to new cohorts	Furthermore, the effect of including interaction terms in the model (ie, testing the assumption of additivity of predictors on the log odds scale) will also be studied. The primary hypothesis under consideration is that >12 inhalations of SABA dosing will have higher odds of CAE risk relative to 0 to 12 inhalations per day. This dosing scheme is consistent with the approved labelling for albuterol inhalation products. Pair-wise interactions will be assessed at the 0.01 significance level to avoid weak interaction signals that would potentially not translate when applying the risk score to new cohorts	This change was made to further explain the analysis model for the endpoints of the study.
Section 15 References (Other sections affected by these changes: Section 2.1.1, 3.3, 9.1)		
~~International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Available at http://www.icmje.org/recommendations/.~~ Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, et al[2]. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. Lancet Respir Med 2013a;1(1):32-42. Patel M, Pilcher J, Reddel HK, Pritchard A, Corin A,	Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, et al[2]. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. Lancet Respir Med 2013a;1(1):32-42. Patel M, Pilcher J, Reddel HK, Pritchard A, Corin A, Helm C, et al. Metrics of salbutamol use as predictors of future adverse outcomes in asthma. Clin Exp Allergy 2013b;43:1144-51.	These changes were made because of new references added to the text and the inadvertent inclusion of a reference that is not cited in the text.

Original text with changes shown	New wording	Reason/justification for change
Helm C, et al. Metrics of salbutamol use as predictors of future adverse outcomes in asthma. Clin Exp Allergy 2013b;43:1144-51.		
Appendix G Product Complaints		
	Added the entire Appendix G - Product Complaints	This appendix was added because of an oversight from the original protocol that should be included.

Appendix A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] Teva Pharmaceuticals [redacted]
Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study	[redacted] Teva Pharmaceuticals [redacted]
Sponsor's Representative of Global Patient Safety and Pharmacovigilance **For serious adverse events:** Send by email to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	[redacted] Teva Pharmaceuticals [redacted]
Contract Research Organization	PRA
Digital Wearable Device Vendor	This information will be provided in the Trial Master File.

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. **Procedures During Screening Visit (Visit 1, Day -14 to Day 1)**

The screening visit (visit 1) will take place not more than 2 weeks before the baseline visit (visit 2) and may occur at the same time as the baseline visit (visit 2). The following procedures will be performed at visit 1:

- obtain written informed consent before any study-related procedures are performed
- review inclusion and exclusion criteria
- assign patient number
- obtain medical history
- obtain prior medication and treatment history
- physical examination, including height and weight
- vital signs measurements, including blood pressure, respiratory rate, and heart rate
- urine pregnancy test for women of childbearing potential
- complete ACQ-5
- inform patients of study compliance for multidose dry powder inhaler with an eModule (eMDPI) and accelerometer, and requirement for provider visit in the event of a clinical asthma exacerbation (CAE)
- assess for asthma exacerbations
- prior and concomitant medication inquiry

2. **Procedures During Intervention Period**

a. Baseline Visit (Visit 2, Day 1)

Patients who meet the inclusion and exclusion criteria at visit 1 may continue to visit 2, when baseline assessments will be conducted (visits 1 and 2 may be combined).

The following procedures will be performed at visit 2:

- review inclusion and exclusion criteria
- inform patients of study compliance for eMDPI and accelerometer, and requirement for provider visit in the event of a CAE
- assess for asthma exacerbations
- inquire about adverse events
- train on use of wearable accelerometers and dispense to the subset of patients who consent to using the devices
- train on the use, collection and accountability of inhaler and dispense albuterol sulfate (ABS) eMDPI

- concomitant medication inquiry

b. Phone Visit (Visits 3 and 4, Days 28±7 days and 56±7 days, respectively)

Patients will be contacted by phone on a monthly basis between visit 2 and visit 3.

The following information will be discussed during the phone call:

- assess for asthma exacerbations and treatments
- inquire about adverse events
- concomitant medication inquiry
- ABS eMDPI dispense, training, collection, and accountability (only Visit 3)
- inform patients of study compliance for eMDPI and accelerometer, and requirement for a provider visit in the event of CAE

c. Final Visit/Early Termination Visit (Visit 5, Day 84 [±14 days])

The following procedures and assessments will be performed at visit 5 or Early Termination Visit:

- urine pregnancy test for women of childbearing potential
- assess for asthma exacerbations
- inquire about adverse events
- collect wearable accelerometer, if applicable
- collect ABS eMDPI
- concomitant medication inquiry

3. **Exacerbation Visit (Vz [+14 days])**

In the case of a CAE (defined in Section 6.1.1 of the protocol), the patient will be required to return to the clinic.The exacerbation visit should be conducted up to 14 days after the clinical asthma exacerbation start date. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

Procedures performed during exacerbation visit include the following:

- physical examination, including weight
- inquire about adverse events
- concomitant medication inquiry

APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol Amendments and Protocol Deviations and Violations

Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

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 may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, objective variable criteria, or Good Clinical Practice (GCP) guidelines; noncompliance to investigational medicinal product (IMP) administration; or use of prohibited medications. Protocol violations will be identified and recorded by investigational center personnel in the case report form (CRF). All protocol violations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the sponsor will determine whether to discontinue the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If the investigational center personnel learns that a patient who did not meet protocol inclusion and exclusion criteria entered the study, they must immediately inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

Information to Study Personnel

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center authorization form, which includes a clear description of each personnel member’s responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form and the study is conducted according to applicable Standard Operating Procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (CRFs and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

APPENDIX D. ETHICS

Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB). All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the informed consent form (ICF), which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original ICFs, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

The investigator, or a qualified person designated by the investigator, should fully inform the patient and parent/legally acceptable representative of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the parent/legally acceptable representative and the patient. The patient and parent/legally acceptable representative should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

A personally signed and dated informed consent form will be obtained from the parent/legally acceptable representative, and a signed and dated assent form will be obtained from each patient (if the patient is able) before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained; according to IEC/IRB requirements. The forms will be signed and dated also by the person who conducted the informed consent discussion. The investigator will keep the original informed consent and assent forms, and copies will be given to the patients (and parent/legally acceptable representative). It will also be explained to the patients (and parent/legally acceptable representative) that they are free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

Adult patients with a legally acceptable representative should provide informed consent according to national and local requirements.

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start at a given investigational

center before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance, or competent authorities. Personal medical information will always be treated as confidential.

Registration of the Clinical Study

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on trials registry websites.

APPENDIX E. WOMEN OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS

Contraception recommendations and pregnancy testing should encompass all investigational medicinal products (IMPs) as well as non-investigational medicinal products, eg, background therapy, and the measures to be followed should be based on the medicinal product with highest risk.

Assessment of likelihood of possible interaction between IMP or concomitant medications and hormonal contraception should be conducted. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method, eg, cytochrome P450 4A inducers. In case of suspected interaction, hormonal contraceptive alone may not be sufficient. In the absence of clinical pharmacokinetic interaction study data in IMPs with demonstrated or suspected human teratogenicity/fetotoxicity, recommendation for use of hormonal contraceptives should be thoroughly justified by the sponsor. Additional contraceptive methods, including supplementary barrier methods, may be considered.

Women of childbearing potential are defined as:

- not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- 1 year postmenopausal (no menses for 12 months without alternative medical cause plus an increased concentration of follicle stimulating hormone [FSH] of more than 35 U/L) in women not using hormonal contraception or hormonal replacement therapy)

Recommendations for application of birth control methods:

- IMPs with Marketing Authorisation (MA)
  - SmPC: In case of no contraception recommendations, the principles of IMPs without MA should be applied
- IMPs without MA
  - All female reproduction toxicity studies and standard battery of genotoxicity tests should be completed prior to the inclusion, in any clinical trial, of women of childbearing potential not using highly effective birth control or whose pregnancy status is unknown (in compliance with International Council for Harmonisation M2)
  - Unavailable or insufficient nonclinical data should be considered as “effects detected” and the highest risk category assumed.
- IMP with demonstrated or suspected human teratogenicity/fetotoxicity
  - Highly effective contraception using methods with low user dependency
  - Contraception during treatment and until the end of relevant systemic exposure. This period should be extended by 30 days in case of genotoxicity.

  - Monthly pregnancy testing to be maintained until end of relevant systemic exposure – should be extended by 30 days in case of genotoxicity. Shorter testing intervals are to be considered depending on drug dosing schedule.

- IMP with possible human teratogenicity/fetotoxicity
  - Highly effective method of contraception
  - Contraception during treatment and until the end of relevant systemic exposure
  - Additional pregnancy testing to be considered; as a minimum, at the end of relevant systemic exposure
  - In each case of delayed menstrual period (over 1 month between menstruations) confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles.
- IMP with unlikely risk of human teratogenicity/fetotoxicity, for which assessment of the completed necessary nonclinical studies does not indicate teratogenicity/fetotoxicity, in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient evidence for lack of risk based on human data
  - An acceptable effective method of contraception unless an absence of risk of human teratogenicity/fetotoxicity in early pregnancy can be justified
  - As a minimum, contraception until treatment discontinuation

Highly effective birth control methods:

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days (for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic) before the first dose of IMP
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 7 days (for IMPs without suspected teratogenicity/genotoxicity) and 1 month (for IMPs potentially teratogenic/genotoxic) before the first dose of IMP
- Intrauterine device and intrauterine hormone-releasing system need to be in place at least 2 months before screening
- Bilateral tubal occlusion and vasectomized partner provided he is the sole sexual partner and has received medical assessment of the surgical process
- Sexual abstinence is **only** considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

- Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are **not** acceptable methods of contraception (according to the Medicines and Healthcare Products Regulatory Agency).

Acceptable birth control methods:

Acceptable birth control methods that result in a failure rate of more than 1% per year include: progestogen-only oral hormonal contraception for which the inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide. The combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, methods of birth control.

Unacceptable birth control methods:

Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

Male contraception:

Male patients must always use a condom, except in cases of no genotoxicity or demonstrated or suspected human teratogenicity/fetotoxicity.

Vasectomy:

Use of contraceptive methods applies also to vasectomized men, because of the risk associated with transfer of a drug via seminal fluid.

Contraception for female partners of male study participants:

Female partners of male study participants must use contraception for non-pregnant woman of childbearing potential partner until the end of relevant systemic exposure in case of IMPs with genotoxicity or IMPs with no genotoxicity but demonstrated or suspected human teratogenicity/fetotoxicity.

Pregnancy tests in women of childbearing potential:

For IMPs with unlikely risk of human teratogenicity/fetotoxicity, additional pregnancy testing is generally not necessary. This refers to IMPs for which assessment of the completed necessary nonclinical studies does not indicate teratogenicity/fetotoxicity in early pregnancy and human data are not available or do not contradict these findings or there is already sufficient evidence for lack of risk based on human data.

APPENDIX F. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of "lost to follow-up."

APPENDIX G. PRODUCT COMPLAINTS

Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient's IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

1. **Product Complaint Information Needed from the Investigational Center**

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No

- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

2. **Handling of Investigational Medicinal Product(s) at the Investigational Center(s)**

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP.

If it is determined that the investigational center must return all IMP, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

3. **Adverse Events or Serious Adverse Events Associated with a Product Complaint**

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5.3, respectively).

4. **Documenting a Product Complaint**

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

APPENDIX H. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the case report form (CRF). Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means, the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, Independent Ethics Committee (IEC)/Institutional Review Board (IRB), and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11 (USA) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources, these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the CRF.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's SOPs for clinical studies. Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the Standard Operating Procedures (SOPs) for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source, and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous or data that are missing will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed informed consent forms
- patient identification lists
- case report forms for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

APPENDIX I. PUBLICATION POLICY

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results: "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (ICMJE). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.