Clinical Study Protocol

CONNected Electronic Inhalers Asthma Control Trial 1 ("CONNECT 1"), a 12-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study to Evaluate the Effectiveness of the Albuterol eMDPI Digital System, to Optimize Outcomes in Patients at Least 13 Years of Age or Older with Asthma

Study Number ABS-AS-40138

NCT03890666

Protocol with Amendment 04 Approval Date: 12 March 2021

Clinical Study Protocol with Amendment 04

Study Number ABS-AS-40138

CONNected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 1 ("CONNECT 1"), a 12-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study to Evaluate the Effectiveness of the Albuterol eMDPI Digital System, to Optimize Outcomes in Patients at Least 13 Years of Age or Older with Asthma

Short title: A 12-Week Treatment Study to Evaluate the Effectiveness of Albuterol eMDPI DS in Patients 13 Years or Older with Asthma

Lay person title**:** A Study to Test if Using the Albuterol eMDPI System is Effective in Getting Better Control of Asthma in Patients at Least 13 Years of Age Compared to Usual Care

Feasibility Study

IND number: 104532; NDA number: Not applicable; 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

Original Protocol Approval Date: 12 October 2018

Protocol with Amendment 04 Approval Date: 12 March 2021

Sponsor

Teva Branded Pharmaceutical
Products R&D, Inc.
145 Brandywine Parkway
West Chester, PA 19380
United States of America

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

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 and Regulations (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

Confidentiality Statement

AMENDMENT HISTORY

The protocol for Study ABS-AS-40138 (original protocol dated 12 October 2018) has been amended and reissued as follows:

Amendment 04	12 March 2021 163 patients randomized/enrolled to date
Amendment 03	30 July 2020 0 patients randomized/enrolled to date
Amendment 02	26 February 2019 0 patients randomized/enrolled to date
Amendment 01	13 December 2018 0 patients randomized/enrolled to date

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

INVESTIGATOR AGREEMENT

Original Protocol Dated 12 October 2018

Protocol with Amendment 04 Approval Date: 12 March 2021

IND number: 104532; NDA number: Not applicable; BLA number: Not applicable; EudraCT number: Not applicable

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Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 04 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 agreement with 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 reporting 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, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations.

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

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted] [redacted] **Global Medical Affairs**		

Executed signature pages are maintained separately within the Trial Master File.

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 12 October 2018

Protocol with Amendment 04 Approval Date: 12 March 2021

IND number: 104532; NDA number: Not applicable; BLA number: Not applicable; EudraCT number: Not applicable

EMA Decision number of Pediatric Investigation Plan: Not applicable

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CONNected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 1 ("CONNECT 1"), a 12-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study to Evaluate the Effectiveness of the Albuterol eMDPI Digital System, to Optimize Outcomes in Patients at Least 13 Years of Age or Older with Asthma

I have read the protocol with Amendment 04 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 agreement with 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 and 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 reporting 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 patient information, IMPs shipment and return forms, and other information collected during the study, in accordance with my responsibilities under the function of the coordinating investigator and in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations. In addition I will assume the responsibility of the coordinating investigator according to a separate contract.

Coordinating Investigator [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Tel: [redacted]

Coordinating Investigator	**Signature**	**Date**
[redacted]		

Executed signature pages are maintained separately within the Investigator Site File and Trial Master File.

CLINICAL STUDY PROTOCOL SYNOPSIS WITH AMENDMENT 04

Study Number ABS-AS-40138

Title of Study: CONNected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 1 ("CONNECT 1"), a 12-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study to Evaluate the Effectiveness of the Albuterol eMDPI Digital System, to Optimize Outcomes in Patients at Least 13 Years of Age or Older with Asthma

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.
145 Brandywine Parkway
West Chester, PA 19380
United States of America (USA)

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 electronic multidose dry powder inhaler (Albuterol eMDPI) Digital System (DS) with 4 component devices:

- Device 1: Albuterol eMDPI
- Device 2: Albuterol eMDPI Patient-facing smart device application (App)
- Device 3: Digital Health Platform (DHP, Cloud solution)
- Device 4: Provider-facing dashboard (dashboard)

Type of Study: Feasibility study to measure the effectiveness of the Albuterol eMDPI DS.

Is this study conducted to investigate the New Use of an approved, marketed product? No

Indications: 1) Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airways disease. 2) Prevention of exercise induced bronchospasm in patients 4 years of age and older.

Number of Investigational Centers Planned: The study is planned to be conducted in approximately 30 investigational centers.

Countries Planned: The study is planned to be conducted in 1 country (USA)

Planned Study Period: The study is expected to start in Q4 2020 and last until approximately Q4 2021.

Number of Patients Planned (total): A total of 330 patients will be enrolled in the study (accounting for 10% early dropouts) and the number of evaluable patients is planned to be 150 in each group.

Study Population: The study population will consist of patients 13 years of age or older with a diagnosis of asthma, currently on an inhaled corticosteroid (ICS) with a long-acting beta$_2$ agonist (LABA), using an albuterol rescue inhaler as part of their existing asthma treatment regimen. Additionally, patients will have uncontrolled or partly controlled asthma quantified as an Asthma Control Test (ACT) score of less than 19 at the screening or baseline visit.

Primary and Secondary Objectives and Endpoints: The primary and secondary study objectives and endpoints are presented in Table 1.

Table 1: Primary and Secondary Study Objectives and Endpoints

Objectives	Endpoints
The **primary objective** of this study is to demonstrate the effectiveness of the DS compared to a concurrent control (CC) group.	The primary endpoint is the proportion of patients for the DS and CC groups achieving meaningful improvement, which is defined as an ACT score greater than or equal to 20 at the end of the 12-week treatment period or an increase of at least 3 units on the ACT score from baseline at the end of the 12-week treatment period.
The **secondary objective (#1)** is to describe the asthma management actions by investigational center health care providers (iHCPs) for all patients in both groups.	This secondary endpoint is the frequency and types of interventions done to improve asthma control including: • number of discussions between patient and iHCP regarding inhaler technique or adherence • number of adjustments of therapy including: o increased or decreased doses of inhaled medication o change to different inhaled medication o additional inhaled medication o addition of a systemic corticosteroid medication for asthma or another controller, including a long-acting muscarinic antagonist (LAMA) or biologics • frequency of intervention to manage comorbid conditions associated with poor asthma control (gastroesophageal reflux disease [GERD], sinusitis, etc.)
The **secondary objective (#2)** is to evaluate short-acting beta$_2$ agonist (SABA) usage and the number of SABA-free days in the DS group.	This secondary endpoint is the change from baseline in the mean weekly SABA usage and the change from baseline in the number of SABA-free days over the 12-week treatment period for the DS group.

Objectives	Endpoints
The **secondary objective (#3)** is to assess the usability and acceptability of the DS by patients in the DS group and the investigational center personnel.	This secondary endpoint is the assessment of the DS (eMDPI, App and dashboard) acceptability and usability, utilizing the System Usability Scale (SUS), completed by the patients in the DS group, 18 years of age or older, and the investigational center personnel at the end of the study.
The **secondary objective (#4)** is to assess behavioral correlates of responsiveness to digital health technology among patients for all patients in both groups.	This secondary endpoint is the assessment of patients' beliefs and perceptions about their disease and treatment, utilizing the Beliefs about Medicines Questionnaire (BMQ) and the Brief Illness Perception Questionnaire (BIPQ) to both the DS and CC groups, patients 18 years of age or older, describing their behavioral profile at baseline and at the end of the study.
The **secondary objective (#5)** is to evaluate the safety of Albuterol eMDPI.	This secondary endpoint is the reporting of adverse events related to Albuterol eMDPI at participating investigational centers. The safety endpoints for this study include the following for all patients in both groups: • adverse event data • adverse device effect data

Notes: The Digital System (DS) group will include eligible study population patients who will use the DS (eMDPI, App, DHP [Cloud solution], and dashboard) during the treatment period. The concurrent control (CC) group will include eligible patients who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period.

Exploratory Objectives and Endpoints:

Exploratory objectives and endpoints are as follows:

General Study Design: This is a 12-week treatment, multicenter, open-label, randomized, parallel group comparison feasibility study to evaluate the effectiveness of the Albuterol eMDPI DS, including inhaler, App, DHP (Cloud solution), and dashboard, to optimize outcomes in patients at least 13 years of age or older with asthma.

The study will consist of a screening/baseline visit (Visit 1), a 12-week open-label treatment period with Visit 2, and a follow-up telephone call (2 weeks following treatment completion).

Patients with suboptimal asthma control will be enrolled in the study and randomized in a 1:1 ratio to 1 of 2 parallel groups stratified by investigational center: DS group patients utilizing the Albuterol eMDPI DS, including inhaler, App, DHP (Cloud solution), and dashboard, and CC group patients who will include eligible patients who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period. Similar data will be collected regarding outcomes for the CC group: ACT after 12 to 14 weeks, BMQ and BIPQ responses, and the frequency of CAEs.

All patients will have a screening/baseline visit (Visit 1), at which they will be asked if they use a smart device and use different applications on their smartphones. A baseline ACT score for all patients, and BMQ and BIPQ responses for patients 18 years of age or older, will be collected. Once randomized, patients in the DS group will be trained on the use of the Albuterol eMDPI DS (including instructions on how to use both the eMDPI and the App) and, upon demonstrating competency, will receive 2 Albuterol eMDPI devices for use as rescue bronchodilators to replace their rescue treatment during the study. Additional Albuterol eMDPI devices may be supplied during the treatment period, based on patients' needs. Patients in the CC group will be reimbursed or given a voucher to use to purchase their existing rescue medications.

Investigational centers will receive similar instruction regarding features of the App, as well as features of the associated dashboard, which mirrors the digital information obtained from the eMDPI and App, including frequency and times of SABA rescue use and associated inspiratory flow parameters measured by the eMDPI with each inhalation.

The CC group will be followed according to the clinical judgment of the investigator; the asthma of patients in the CC group will be managed in a manner consistent with the clinical judgement of the investigator and based on asthma management guidelines (eg, GINA). Similar to the management of the CC group, the DS group patients will be followed by the investigational centers with the addition of objective information on Albuterol eMDPI usage being available to both patients and investigational centers through the App and the dashboard, respectively. The iHCPs will check the dashboard at least once a week and use this information, as per their clinical judgment, to modify patients' asthma management. Clinically Driven Assessments for both groups, if necessary, should be arranged per the clinical judgement of the iHCP managing the patient and can be via a telephone call or an on-site visit.

For all patients, at Visit 2 and at each Clinically Driven Assessment, the iHCP will record answers to Asthma Management questions, including discussions regarding adherence, or inhaler technique, treatment adjustments, or additions of new treatments, including biologic medication usage. Additionally, in the case of a Clinically Driven Assessment, (for patients in the DS group), the iHCP will be asked whether or not the contact with the patient was originated from the iHCP interaction with the dashboard.

At the end of the treatment period (12 weeks), final assessments of the DS and CC group patients will be made, as specified in Table 3. A follow-up telephone call will be made by the investigational center to all patients, 2 weeks later, and will confirm the DS group patients have returned to previous asthma treatments.

It should also be noted that no specific clinical decisions are being mandated. One secondary objective of this study is to describe how clinicians actually use the information provided by the DS to manage their patients.

Study procedures and assessments with their time points are shown in Table 3. The study schematic diagram is shown in Figure 2.

Method of Randomization and Blinding:

Patients will be randomly assigned to the DS group or CC group in a 1:1 ratio stratified by investigational center, respectively, using a Randomization and Trial Supply Management (RTSM) system.

This is an open-label study, and therefore, blinding is not applicable.

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

Test IMP:

Albuterol eMDPI DS with 4 components:

- Device 1: Albuterol eMDPI
- Device 2: Albuterol eMDPI Patient-facing smart device App
- Device 3: DHP (Cloud solution)
- Device 4: Provider-facing dashboard (dashboard)

Investigational medicinal products are defined as test IMP, reference IMP, and placebo IMP (Table 2).

Table 2: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP	Reference IMP
Trade name and INN, if applicable, or company-assigned number	Albuterol eMDPI	None	None
Formulation	Oral inhalation powder	NA	NA
Unit dose strength(s)/Dosage level(s)	117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base) from the device reservoir to provide a delivered dose of 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base)	NA	NA
Route of administration	Oral inhalation	NA	NA

Table 2: Investigational Medicinal Products Used in the Study (Continued)

IMP name	Test IMP	Placebo IMP	Reference IMP
Dosing instructions/Dosing schedule/Titration periods/Treatment periods	1 to 2 oral inhalations every 4 to 6 hours, as needed	NA	NA
Packaging	NA	NA	NA
Manufacturer	Teva Pharmaceutical Industries, Ltd. Jerusalem, Israel, or Teva Pharmaceuticals Ireland, Waterford, Ireland	NA	NA

Albuterol eMDPI=albuterol sulfate electronic dry powder inhaler; IMP=investigational medicinal product; INN=International Nonproprietary Name; NA=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. However, as the dosing of the test IMP is on an as-needed basis, there is no set maximum exposure.

Study Duration: Approximately 12 months (from Q4 2020 to Q4 2021)

End of Study: End of study is defined as the follow-up telephone call for the last patient.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: No treatment is planned after the end of the study; DS patients will be placed back on their usual SABA rescue therapy at treatment end and follow up through their iHCPs.

Selection of Patients/Study Population

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

a. The patient is 13 years or older at the time of screening.

b. The patient has a documented diagnosis of asthma established at the investigational center at the time of informed consent or the investigator confirms a diagnosis of asthma.

c. The patient is currently on treatment with an ICS with a LABA.

d. The patient has an ACT score of less than 19 at the screening or baseline visit.

e. The patient is currently using inhaled albuterol sulfate as rescue medication and is willing to discontinue all other rescue medications and replace them with the study-provided Albuterol eMDPI.

f. [Revision 1] The patient can read and communicate in English and is familiar with and is willing to use his/her own smart device that meets the minimum App requirements and download and use the App.

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

h. The patient must be willing and able to comply with study requirements and restrictions and to remain at the investigational center for the required duration during

the study period, and willing to return to the investigational center for the follow-up procedures and assessments as specified in this protocol.

Exclusion Criteria: Patients will be excluded from participating in this study if they meet any of the following criteria:

a. The patient has any clinically significant uncontrolled medical condition (treated or untreated) other than asthma, which in the view of the investigator would preclude participation.

b. The patient was hospitalized for severe asthma in the last 30 days.

c. The patient has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.

d. The patient has a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) or Asthma-COPD Overlap (ACO).

e. The patient is a current smoker or has a greater than 10 pack-year history of smoking.

f. The patient is currently being treated with systemic corticosteroids (oral, intramuscular, or intravenous) or has been treated within the last 30 days.

g. [Revision 1] The patient has any treatment with biologics for asthma (eg, omalizumab, anti-interleukin (IL) 5, anti-IL5R, anti-IL4R), or has had such treatment within the last 90 days. However, during the study, patients can be escalated to therapy with such agents if clinically indicated in the judgment of the investigator as part of their asthma management and remain in the study.)

h. The patient has a known hypersensitivity to any components of the IMPs stated in this protocol.

i. [New criterion] The patient has previously participated in a Digihaler study or is currently being treated prior to enrollment with a digital inhaler system, including the Digihaler system or an external "bolt on" digital system designed to monitor inhaler usage, such as the Propeller Health or Adherium systems.

Statistical Considerations

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 in the clinical study report (CSR).

Sample Size Rationale:

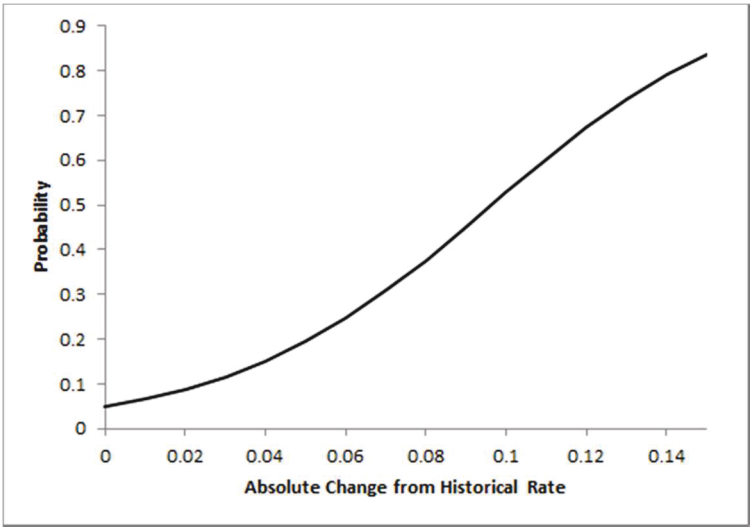
Sample size estimates are based upon the assumption that the absolute differences between the DS and CC groups and the associated operational characteristics will be similar to the absolute differences and operational characteristics of the DS and CC groups noted in the sample size rationale for the study design.

The recommended sample size for the study is 150 evaluable patients per group (30 investigational centers, with each investigational center enrolling at least 10 patients), 300 patients in total. Accounting for a dropout rate of 10%, this leads to a recommended total number of 330 enrolled patients.

With this sample size and assuming a true absolute difference in proportions (treatment effect as the estimated response rate for the CC group is 60% and for the DS group is 73%) between the groups of at least 13%, the probability that the posterior probability will be at least 95% is 0.77 (power) (analogous to 1-sided p-value < 0.05). Assuming no treatment effect (difference in proportions between the groups is 0%, ie, Type 1 error), then the probability that posterior probability will be at least 95% is 0.05.

It should be noted that both power and Type 1 error are dependent on the absolute difference between the DS and the CC groups as illustrated in Figure 1 below by the operational characteristics calculated for the study design:

Figure 1: Operational Characteristics Calculated for the Study Design



Analysis Sets

Intent-to-Treat Analysis Set (ITT)

The intent-to-treat (ITT) analysis set will include all randomized patients. In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. This analysis population will be used for summarization of patient disposition and demographic and baseline characteristics, as appropriate.

Modified Intent-to-Treat Analysis Set (mITT)

The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP (IMP is albuterol eMDPI for the DS group and standard-of-care albuterol-administering rescue medication for the CC group) and at least 1 postbaseline assessment on any of the study endpoints (primary, secondary, or exploratory).

In the mITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. This analysis will be used for all primary, secondary, and exploratory endpoint analyses.

Safety Analysis Set

This analysis set will include all patients in the DS group who receive at least 1 dose of IMP and all patients in the CC group. In the safety analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified. This analysis set will be used for all safety analyses.

Additional analysis sets may be defined in the Statistical Analysis Plan, if appropriate.

Analysis

Primary Analysis:

The primary endpoint is the proportion of patients reaching well-controlled asthma as defined by an ACT score of greater than or equal to 20 or a clinically important improvement in asthma control as defined by an increase of at least 3 units on the ACT score from baseline at the end of the 12-week treatment period (responder analysis of DS versus CC group with responders defined by an ACT score of greater than or equal to 20 or an increase by greater than or equal to 3 units on the ACT score).

Estimand framework:

1. Analysis will be performed on the mITT set.
2. A binary distribution is assumed for the primary endpoint. Patients who discontinue early due to technology failure, disliking the digital platform, disease worsening, adverse experience or disliking the IMP will be counted as treatment failures. For those who discontinue early not due to these reasons, the ACT value assessed at the Early Termination (ET) visit will be used.
3. Summary measure: A successful differentiation between the 2 groups will be determined by a Bayesian posterior probability for $\beta_1 > 0$ greater than 0.95 (1-sided). The following statistical methods will be utilized:

Logistic regression model allowing for different response rates at enrolling investigational centers will be used for testing the hypothesis $H_0: \beta_1 = 0$, $H_1: \beta_1 > 0$ in the following model:

$$ln\frac{p_{ij}}{1-p_{ij}} = \delta_j + \beta_0 baseline\ ACT\ value + \beta_1 x_{ij}$$

where i = treatment group, j = investigational center, x_{ij} = treatment group i for investigational center j, p_{ij} = response proportion of treatment group i in investigational center j.

Non-informative priors will be assumed for all coefficients.

Estimates of odds ratio and individual proportions with corresponding credible intervals will be presented.

Sensitivity Analysis: If appropriate, sensitivity analyses will be specified in the Statistical Analysis Plan.

Secondary Analysis:

All secondary endpoints will be based on the mITT analysis set and analyzed descriptively.

For continuous variables, descriptive statistics (number [n], mean, standard deviation, median, minimum, and maximum) will be provided for observed values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

Other Analysis: NA

Analysis of Exploratory/Other Endpoints:

[redacted]

Multiple Comparisons and Multiplicity:
Since there is only 1 primary endpoint-based statistical analysis and the multiple secondary endpoints will be analyzed using descriptive statistical analysis techniques, no adjustments for multiple comparisons/multiplicity will be made for the preplanned multiple comparisons/endpoints.

Safety Analyses: Safety analyses will be performed on the safety analysis set.

Safety assessments and time points are provided in Table 3.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term (PT) or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious adverse events, adverse events causing withdrawal from the study, and adverse device effects. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in vital signs measurements data will be summarized descriptively. All values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.

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

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for observed 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, adverse device effects, and potentially clinically significant abnormal values (vital signs) 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.

Planned Interim Analysis: There will be no formal interim analysis.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
ACO	Asthma- chronic obstructive pulmonary disease (COPD) Overlap
ACT	Asthma Control Test
App	smart device application
BIPQ	Brief Illness Perception Questionnaire
BLA	Biological License Application
BMQ	Beliefs about Medicines Questionnaire
CAE	clinical asthma exacerbation
CC	concurrent control
CFR	Code of Federal Regulations (USA)
COPD	chronic obstructive pulmonary disease
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
DHP	Digital Health Platform
DS	Digital System
ED	emergency department
EIB	exercise-induced bronchospasm
EMA	European Medicines Agency
eModule	electronic module
eMDPI	multidose dry powder inhaler with integrated electronic module
ET	Early Termination
EU	European Union
EudraCT	European Clinical Trials
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GINA	Global Initiative for Asthma
GPSP	Global Patient Safety and Pharmacovigilance
IB	Investigator's Brochure
ICF	informed consent form
ICH	The International Council on Harmonisation
ICS	inhaled corticosteroid

Abbreviation	Term
IEC	Independent Ethics Committee
iHCP	investigational center healthcare provider
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
iOS	iPhone operating system
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	intent-to-treat
LABA	long-acting $beta_2$ agonist
LAMA	long-acting muscarinic antagonist
LSO	local safety officer
MDI	metered dose inhaler
MDPI	multidose dry powder inhaler
MID	minimally important difference
mITT	modified intent-to-treat
NDA	New Drug Application
NIH	National Institute of Health
PRO	patient-reported outcome
PT	preferred term
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
SABA	short-acting $beta_2$ agonists
SOP	Standard Operating Procedure
SUS	System Usability Scale
SUSAR	suspected unexpected serious adverse reaction
SOC	system organ class
US/USA	United States (of America)
WHO	The World Health Organization
WHO Drug	World Health Organization Drug Dictionary

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

Asthma is one of the most common chronic diseases. This is a heterogeneous condition that often affects the airway passages of the lungs and is characterized by airway inflammation and bronchial hyper-responsiveness that vary over time in their occurrence, frequency, and intensity. 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. It is believed that these asthma symptoms, in association with suboptimal treatment or aging, may lead to chronic changes in airway structure and function, increasing the morbidity and mortality of those affected (Global Initiative for Asthma [GINA] 2018).

As the recommended drug for relief of acute asthmatic symptoms and as the prophylaxis for exercise-induced bronchoconstriction, short-acting beta$_2$ agonists (SABAs), such as albuterol, are a mainstay of asthma management. Albuterol sulfate 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]. 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.

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 developed the breath-actuated inhaler PROAIR® RESPICLICK® (albuterol sulfate inhalation powder), which utilizes a formulation blend of albuterol sulfate 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).

PROAIR RESPICLICK has been available in the United States (US) since March 2015. It is indicated for treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm in patients 4 years of age and older.

On 21 December 2018, the US Food and Drug Administration (FDA) approved Albuterol multidose dry powder inhaler (MDPI) with an integrated electronic module (eMDPI) as PROAIR® DIGIHALER™ (albuterol sulfate inhalation powder), 90 mcg of albuterol base per actuation, for the same indication as PROAIR RESPICLICK. PROAIR DIGIHALER contains a built-in electronic module (eModule; ie, the Digihaler) that detects, records, and stores data on inhaler events for transmission to a mobile application (App). More detailed prescribing information for this product may be found in the Investigator’s Brochure (IB).

In this study, 90 mcg of albuterol sulfate is delivered via PROAIR DIGIHALER. Teva has developed the eModule (ie, the Digihaler) as part of a Digital System (DS) to assist a patient with

asthma to appropriately use the eMDPI inhaler. The system is described in more practical terms as an inhaler with integrated data logger capable of storing and transmitting timestamped data. The information from the eModule will be transmitted wirelessly (Bluetooth Low Energy) to the smart device App. From the App, data may be transmitted to the Digital Health Platform (DHP), which consists of a Cloud solution, and then to a provider-facing dashboard. The DHP is used to provide patient-specific data to the iHCP via the dashboard, a secure web interface. The following devices will be evaluated in this study:

Device 1: The Albuterol eMDPI, which is the test investigational medicinal product (IMP)

Device 2: Patient-facing App

Device 3: DHP (Cloud solution)

Device 4: Provider-facing dashboard

The purpose of the study is to evaluate whether outcomes for patients using the Albuterol eMDPI DS can be optimized better than a concurrent control (CC) group who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period. The study will also assess mean weekly SABA usage and the number of SABA-free days, the asthma management actions of investigational heath care providers (iHCPs) using the dashboard as part of the DS, and will collect information using patient questionnaires that focus on patients' beliefs and perceptions about their disease and inhaler satisfaction, as well as patient and investigational center personnel questionnaires on system usability.

1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of the clinical studies are provided in this section.

Bronchospasm Associated with Asthma: In two 12-week, randomized, double-blind, placebo-controlled studies of identical design (Study 1 and Study 2), albuterol sulfate MDPI (153 patients) was compared to a matched placebo dry powder inhaler (163 patients) in asthmatic patients 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 albuterol sulfate MDPI 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. Consistent results were observed in Study 2. In a double-blind, randomized, placebo-controlled, single-dose, crossover study evaluating albuterol sulfate MDPI and PROAIR® HFA[1] in 71 adult and adolescent patients 12 years of age and older with persistent asthma, albuterol sulfate MDPI 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 albuterol sulfate MDPI 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

[1] PROAIR® HFA is a registered trademark of Teva Respiratory, LLC.

38) of patients as compared to 42% (16 of 38) of patients when they received placebo. Patients who participated in these clinical studies were allowed to use concomitant steroid therapy.

More detailed information is provided in the IB.

Clinical Safety: A total of 1289 subjects were treated with albuterol sulfate MDPI 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 albuterol sulfate MDPI 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.

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(s)

This open-label study is being undertaken to evaluate whether outcomes for patients using the Albuterol eMDPI DS can be optimized better than a CC group who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period. In addition to assessing the technical reliability experienced by patients using the Albuterol eMDPI DS, the study also uses 2 patient questionnaires, the Beliefs about Medicines Questionnaire (BMQ) and the Brief Illness Perception Questionnaire (BIPQ) for all patients, 18 years of age or older, in both groups, as well as the System Usability Scale (SUS) for patients, 18 years of age or older, in the DS group and investigational center personnel to complete.

Albuterol eMDPI is a rescue/reliever agent that includes an eModule on top of the approved PROAIR RESPICLICK inhaler. The Albuterol eMDPI DS consists of the Albuterol eMDPI, the App, the Cloud solution, and the dashboard. The Albuterol eMDPI can be used with or without the additional devices (App, Cloud solution, and dashboard) that are being evaluated in this study. The on-board electronics and power source in the eMDPI are fully integrated into the inhaler and are designed to operate for the life of the inhaler without intervention. The eModule records timestamped pre-defined events. The inclusion of the eModule has been shown to have no impact on the dose delivery compared with the approved product without the eModule (performance and functional testing on file at Teva). Additional information regarding benefits and risks of Albuterol eMDPI to patients may be found in the IB.

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of this study is to demonstrate the effectiveness of the DS compared to a CC group.	The primary endpoint is the proportion of patients for the DS and CC groups achieving meaningful improvement, which is defined as an Asthma Control Test (ACT) score greater than or equal to 20 at the end of the 12-week treatment period or an increase of at least 3 units on the ACT score from baseline at the end of the 12-week treatment period.
The **secondary objective (#1)** is to describe the asthma management actions by iHCPs for all patients in both groups.	This secondary endpoint is the frequency and types of interventions done to improve asthma control including: • number of discussions between patient and iHCP regarding inhaler technique or adherence • number of adjustments of therapy including: o increased or decreased doses of inhaled medication o change to different inhaled medication o additional inhaled medication o addition of a systemic corticosteroid medication for asthma or another controller, including a long-acting muscarinic antagonist (LAMA) or biologics • frequency of intervention to manage comorbid conditions associated with poor asthma control (gastroesophageal reflux disease [GERD], sinusitis, etc.)
The **secondary objective (#2)** is to evaluate SABA usage and the number of SABA-free days in the DS group.	This secondary endpoint is the change from baseline in the mean weekly SABA usage and the change from baseline in the number of SABA-free days over the 12-week treatment period for the DS group.

Objectives	Endpoints
The **secondary objective (#3)** is to assess the usability and acceptability of the DS by patients in the DS group and the investigational center personnel.	This secondary endpoint is the assessment of the DS (eMDPI, App and dashboard) acceptability and usability, utilizing the SUS, completed by the patients in the DS group, 18 years of age or older, and the investigational center personnel at the end of the study.
The **secondary objective (#4)** is to assess behavioral correlates of responsiveness to digital health technology among patients for all patients in both groups.	This secondary endpoint is the assessment of patients' beliefs and perceptions about their disease and treatment, utilizing the BMQ and the BIPQ to both the DS and CC groups, patients 18 years of age or older, describing their behavioral profile at baseline and at the end of the study.
The **secondary objective (#5)** is to evaluate the safety of Albuterol eMDPI.	This secondary endpoint is the reporting of adverse events related to Albuterol eMDPI at participating investigational centers. The safety endpoints for this study include the following for all patients in both groups: • adverse event data • adverse device effect data

Notes: The Digital System (DS) group will include eligible study population patients who will use the DS (eMDPI, App, DHP [Cloud solution], and dashboard) during the treatment period. The concurrent control (CC) group will include eligible patients who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period.

2.1.1. Justification of Primary Endpoint

Current asthma guidelines emphasize that asthma symptom control is a key therapeutic goal and recommend assessments of asthma control as a guide to step therapy. The ACT has been recommended by the National Institute of Health (NIH) as useful objective scoring system to measure asthma symptom control as a measure of core outcomes for both clinical trials and observational studies (Cloutier et al 2012). ACT scores indicating poorer symptom control have been associated with higher risk of asthma exacerbations as well as asthma related health care resource utilization (Ko et al 2012). In general, an ACT score of greater than 20 indicates well-controlled asthma (Nathan et al 2004) and the minimally important difference (MID) that represents a clinically significant change in ACT has been demonstrated to be 3 units (Schatz et al 2009).

2.2. Exploratory Objectives and Endpoints

Exploratory objectives and endpoints are as follows:

[redacted]

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a 12-week treatment, multicenter, open-label, randomized, parallel group comparison feasibility study to evaluate the effectiveness of the Albuterol eMDPI DS, including inhaler, App, DHP (Cloud solution), and dashboard, to optimize outcomes in patients at least 13 years of age or older with asthma.

The study will consist of a screening/baseline visit (Visit 1), a 12-week open-label treatment period with Visit 2, and a follow-up telephone call (2 weeks following treatment completion).

Patients with suboptimal asthma control will be enrolled in the study and randomized in a 1:1 ratio to 1 of 2 parallel groups stratified by investigational center: DS group patients utilizing the Albuterol eMDPI DS, including inhaler, App, DHP (Cloud solution), and dashboard, and CC group patients who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period. Similar data will be collected regarding outcomes for the CC group: ACT after 12 to 14 weeks, BMQ and BIPQ responses, and the frequency of CAEs.

All patients will have a screening/baseline visit (Visit 1), at which they will be asked if they use a smart device and use different applications on their smart devices. A baseline ACT score for all patients, and BMQ and BIPQ responses for patients 18 years of age or older, will be collected. Once randomized, patients in the DS group will be trained on the use of the Albuterol eMDPI DS (including instructions on how to use both the eMDPI and the App) and, upon demonstrating competency, will receive 2 Albuterol eMDPI devices for use as rescue bronchodilators to replace their rescue treatment during the study. Additional Albuterol eMDPI devices may be supplied during the treatment period, based on patients' needs. Patients in the CC group will be reimbursed or given a voucher to use to purchase their existing rescue medications.

Investigational centers will also receive similar instruction regarding features of the App, as well as features of the associated dashboard, which mirrors the digital information obtained from the eMDPI and App, including frequency and times of SABA rescue use and associated inspiratory flow parameters measured by the eMDPI with each inhalation.

The CC group will be followed according to the clinical judgment of the investigator; the asthma of patients in the CC group will be managed in a manner consistent with the clinical judgement of the investigator and based on asthma management guidelines (eg, GINA). Similar to the management of the CC group, the DS group patients will be followed by the investigational centers with the addition of objective information on Albuterol eMDPI usage being available to both patients and investigational centers through the App and the dashboard, respectively. The iHCPs will check the dashboard at least once a week and use this information, as per their clinical judgment, to modify patients' asthma management. Clinically Driven Assessments for both groups, if necessary, should be arranged per the clinical judgement of the iHCP managing the patient and can be via a telephone call or an on-site visit.

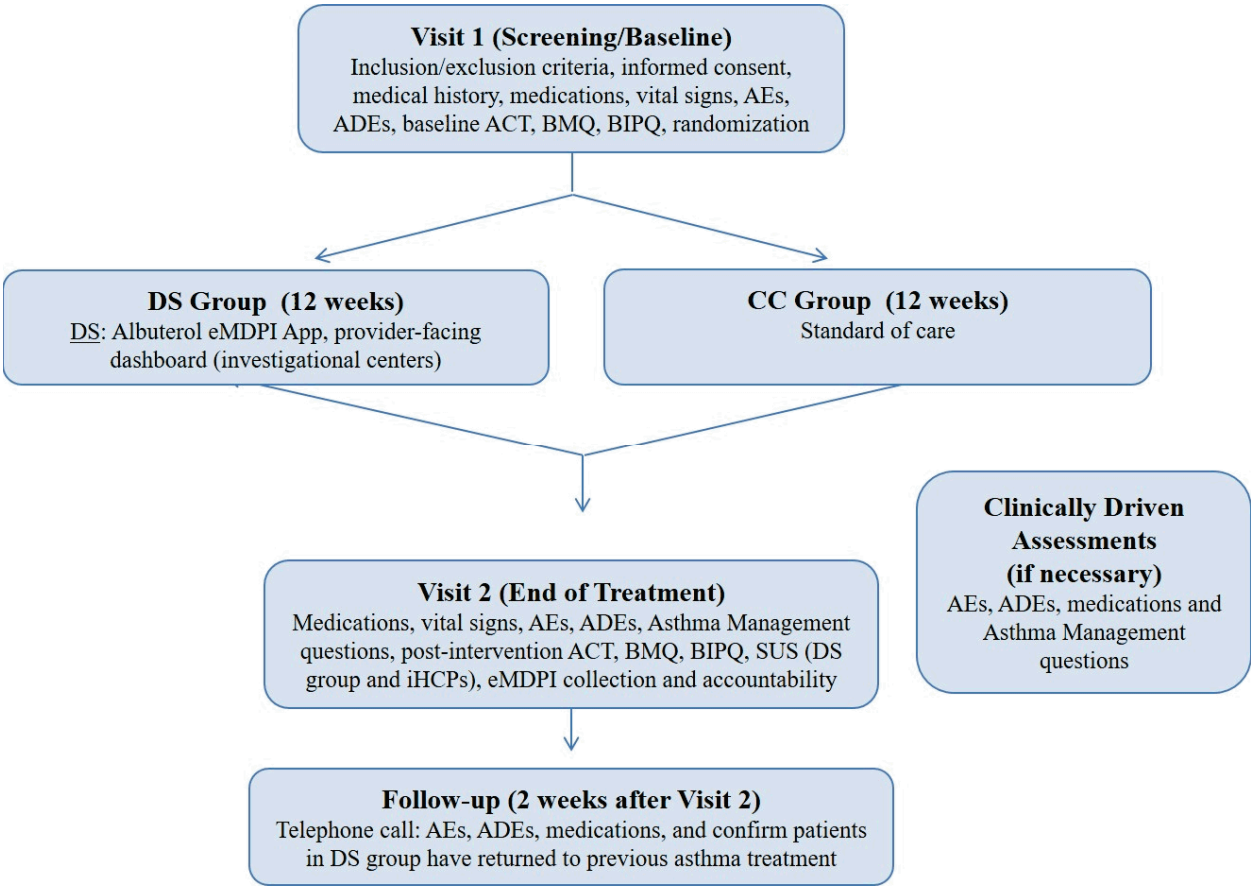
For all patients, at Visit 2 and at each Clinically Driven Assessment, if necessary, the iHCP will record answers to Asthma Management questions, including discussions regarding adherence, or inhaler technique, treatment adjustments, or additions of new treatments, including biologic medication usage. Additionally, in the case of a Clinically Driven Assessment (for patients in the

DS group), the iHCP will be asked whether or not the contact with the patient was originated from the iHCP interaction with the dashboard.

At the end of the treatment period (12 weeks), final assessments of the DS and CC group patients will be made, as specified in Table 3. A follow-up telephone call will be made by the investigational center to all patients, 2 weeks later, and will confirm the DS group patients have returned to previous asthma treatments.

It should also be noted that no specific clinical decisions are being mandated. One secondary objective of this study is to describe how clinicians actually use the information provided by the DS to manage their patients.

Figure 2: Overall Study Schematic Diagram



ACT=Asthma Control Test; ADEs=adverse device effects; AEs=adverse events; Albuterol eMDPI=albuterol sulfate electronic multidose dry powder inhaler; BIPQ=Brief Illness Perception Questionnaire; BMQ= Beliefs about Medicines Questionnaire; CC=concurrent control; DS=Digital System; iHCPs=investigational center health care providers; SUS=System Usability Scale.
Note: The BIPQ, BMQ, and SUS questionnaire will be completed by patients 18 years of age or older.

3.2. Planned Number of Patients and Countries

A total of 330 patients will be enrolled in the study (accounting for 10% early dropouts) and the total number of evaluable patients is planned to be 300 (150 in each group). Details on definition of evaluable patients and sample size are given in Section 9.1.

The study is planned to be conducted in the US in approximately 30 investigational centers. The study is expected to start in Q4 2020 and last until approximately Q4 2021.

3.3. Justification for Study Design and Selection of Population

Sample size estimates are based upon the assumption that the absolute differences between the DS and CC groups and the associated operational characteristics will be similar to the absolute differences and operational characteristics of the DS and CC groups noted in the sample size rationale for the study design.

The population for the study was chosen based on level of asthma control, as the objective of the study is to assess potential improvement in asthma control with the Albuterol eMDPI DS.

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 (Section 7.1.5) as they are reported from the investigational centers to identify safety concerns.

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 the following:

- new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the IMP or device

If the whole study is stopped, patients who 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 3. Detailed descriptions of each method of procedures and assessments are provided in Section 6 (efficacy assessments) and Section 7 (safety assessments). Study procedures and assessments by visit are listed in Appendix B.

Table 3: Study Procedures and Assessments

Study period	**Screening/ Baseline visit**	**Treatment period (12 weeks)**	**Follow-up telephone call[a]**	**Clinically Driven Assessment(s) (if necessary)**	**Unscheduled IMP dispensing visit**
		End of Treatment/Early Termination visit			
Visit number	**Visit 1**	**Visit 2**			
Day and allowed time windows	**Day 1[b]**	**Day 84 + 7 days**	**Day 98 + 7 days**		
Procedures and assessments					
Informed consent/assent	X				
Inclusion and exclusion criteria	X				

Study period	**Screening/ Baseline visit**	**Treatment period (12 weeks)**	**Follow-up telephone call[a]**	**Clinically Driven Assessment(s) (if necessary)**	**Unscheduled IMP dispensing visit**
		End of Treatment/Early Termination visit			
Visit number	**Visit 1**	**Visit 2**			
Day and allowed time windows	**Day 1[b]**	**Day 84 + 7 days**	**Day 98 + 7 days**		
Procedures and assessments					
Medical history	X				
Current medication and treatment history related to asthma	X				
Inform patients of study restrictions and compliance requirements	X				
ACT score[c]	X	X			
BMQ and BIPQ[c]	X	X			
Assign patient number and provide unique email account for DS group patients	X				
Train and Dispense Test IMP to DS group[d]	X			X[e]	X
Registration and Onboarding (App)	X				
Adverse events and adverse device effects inquiry	X	X	X	X	X
Vital signs measurement	X	X			
iHCP will ask Asthma Management questions regarding adherence, inhaler technique, treatment adjustments, and biologic medication usage		X		X	
Administer post-intervention PRO questionnaire (SUS) to DS group patients and investigational center personnel[f]		X			
Concomitant medication inquiry	X	X	X	X	X

Table 3: Study Procedures and Assessments (Continued)

Study period	Screening/ Baseline visit	Treatment period (12 weeks)	Follow-up telephone call[a]	Clinically Driven Assessment(s) (if necessary)	Unscheduled IMP dispensing visit
		End of Treatment/Early Termination visit			
Visit number	**Visit 1**[b]	**Visit 2**			
Day and allowed time windows	**Day 1**	**Day 84 + 7 days**	**Day 98 + 7 days**		
Procedures and assessments					
Test IMP collection and accountability		X			X
Remove App from the patient's smart device		X			
Confirmation that patient has returned to previous asthma treatment			X[g]		

[a] End of study is defined as the follow-up telephone call for the last patient.

[b] Screening and enrollment are expected to occur on the same day. The maximum allowable duration between screening and enrollment is 7 days.

[c] ACT is to be completed first by all patients, followed by the BMQ, and then the BIPQ (both by patients 18 years of age or older).

[d] Patients will be provided the Test IMP, along with training on use and proper technique, by the investigational centers.

[e] If on-site and necessary.

[f] The SUS should be the last questionnaire provided to patients, 18 years of age or older, at the end of treatment visit or at the Early Termination (ET) visit. Each investigational center will receive 1 SUS questionnaire to complete following the last patient visit at the investigational center.

[g] The follow-up telephone call will be made to all patients, including those who end the study prematurely (except patients who withdraw consent). If a patient in the DS group ends the study prematurely, in addition to following up on ongoing AEs and concomitant medications, the investigational center will also confirm that the patient has returned to their previous asthma treatment.

ACT=Asthma Control Test; App=smart device application; BIPQ=Brief Illness Perception Questionnaire; BMQ=Beliefs about Medicines Questionnaire; DS=digital system; ET=early termination; iHCP=investigational center health care provider; IMP=investigational medicinal product; PRO=patient-reported outcome; SUS=System Usability Scale.

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).

Changes to inclusion or exclusion criteria are detailed in Section 16.

4.1. Patient Inclusion Criteria

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

a. The patient is 13 years or older at the time of screening.

b. The patient has a documented diagnosis of asthma established at the investigational center at the time of informed consent or the investigator confirms a diagnosis of asthma.

c. The patient is currently on treatment with an ICS with a long-acting beta$_2$ agonist (LABA).

d. The patient has an ACT score of less than 19 at the screening or baseline visit.

e. The patient is currently using inhaled albuterol sulfate as rescue medication and is willing to discontinue all other rescue medications and replace them with the study-provided Albuterol eMDPI.

f. [Revision 1] The patient can read and communicate in English and is familiar with and is willing to use his/her own smart device that meets the minimum App requirements and download and use the App.

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

h. The patient must be willing and able to comply with study requirements and restrictions and to remain at the investigational center for the required duration during the study period, and willing to return to the investigational center for the follow-up procedures and assessments as specified in this protocol.

4.2. Patient Exclusion Criteria

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

a. The patient has any clinically significant uncontrolled medical condition (treated or untreated) other than asthma, which in the view of the investigator would preclude participation.

b. The patient was hospitalized for severe asthma in the last 30 days.

c. The patient has any medical or psychiatric condition that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.

d. The patient has a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) or Asthma-COPD Overlap (ACO).

e. The patient is a current smoker or has a greater than 10 pack-year history of smoking.

f. The patient is currently being treated with systemic corticosteroids (oral, intramuscular, or intravenous) or has been treated within the last 30 days.

g. [Revision 1] The patient has any treatment with biologics for asthma (eg, omalizumab, anti-interleukin (IL) 5, anti-IL5R, anti-IL4R), or has had such treatment within the last 90 days. (However, during the study, patients can be escalated to therapy with such agents if clinically indicated in the judgment of the investigator as part of their asthma management and remain in the study.)

h. The patient has a known hypersensitivity to any components of the IMPs stated in this protocol.

i. [New criterion] The patient has previously participated in a Digihaler study or is currently being treated prior to enrollment with a digital inhaler system, including the Digihaler system or an external "bolt on" digital system designed to monitor inhaler usage, such as the Propeller Health or Adherium systems.

4.3. Withdrawal Criteria and Procedures for the Patient

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

1. Patient withdraws consent or requests discontinuation from the IMP or withdrawal from the study for any reason.
2. Patient develops an illness that would interfere with his/her continued participation.
3. Patient is noncompliant with the study procedures and assessments or administration of Albuterol eMDPI, in the opinion of the investigator.
4. Patient takes prohibited concomitant medications as defined in this protocol (ie, other SABA products).
5. The sponsor requests withdrawal of the patient.
6. Patient experiences an adverse event or other medical condition which 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 from the study or discontinuation from IMP. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study or discontinuation from IMP, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal from the study or discontinuation from IMP.

See Appendix E 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 from the study or discontinuation from IMP is an adverse event and/or adverse device effect, 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; the adverse events page and/or adverse device effect page and the termination page of the CRF will be completed at that time. The investigator must inform the contract research organization (CRO) as soon as possible of each patient who is being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study or discontinues IMP for multiple reasons that include adverse events, the relevant page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be "need to take a prohibited medication," not the adverse event.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records and transcribed to the CRF.

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

4.4. Replacement of Patients

A patient who is enrolled but does not complete the treatment period will not be replaced.

4.5. Rescreening

A patient who is screened but not enrolled within 7 days of screening, because he/she did not satisfy inclusion/exclusion criteria or enrollment did not occur within the specified time, may be considered for rescreening once if, for example, there is a change in the patient's medical background or a modification of study inclusion and exclusion criteria.

Patients may have individual parameters retested at the discretion of both the investigator and the sponsor.

If the patient is rescreened, the informed consent form (ICF) will need to be re-signed.

4.6. Screening Failure

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. 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

The Teva eMDPI Digital System consists of 4 devices. Device 1 is the Albuterol eMDPI, which is the test IMP. The 3 investigational medical devices are the following:

Device 2: Patient-facing App

Device 3: DHP (Cloud solution)

Device 4: Provider-facing dashboard

At Visit 1, patients in the DS group will be trained on the use of the Albuterol eMDPI DS (including instructions on how to use both the eMDPI and the App) and, upon demonstrating competency, will receive 2 Albuterol eMDPI devices for use as rescue bronchodilators to replace their rescue treatment during the study. Additional Albuterol eMDPI devices may be supplied during the treatment period, based on patients' needs. Patients will be instructed to return all inhalers to the investigational center at the end of treatment visit or at early termination.

5.1.1. Test Investigational Medicinal Product

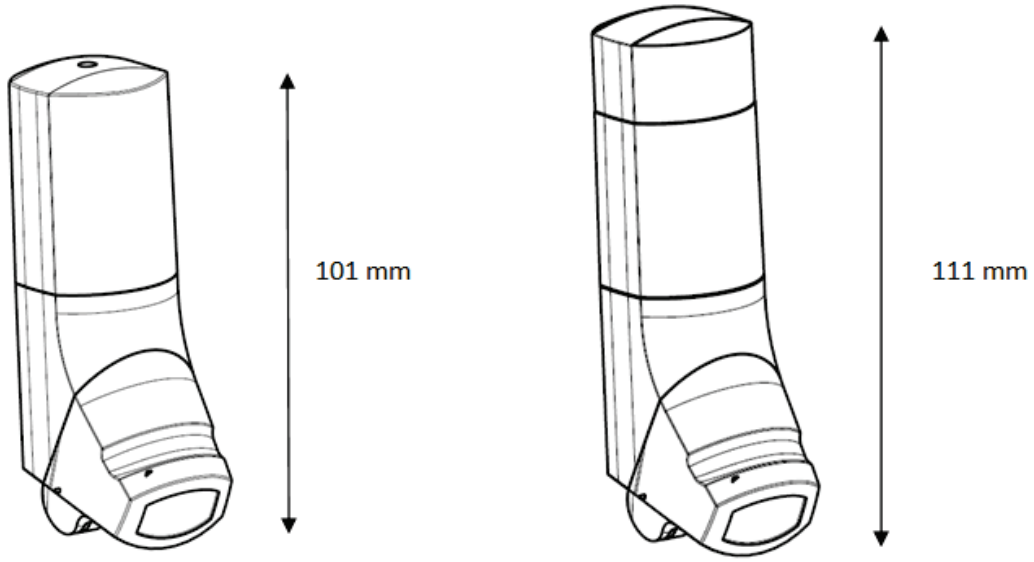
Albuterol eMDPI (marketed in the US as PROAIR DIGIHALER) is an inhalation-driven eMDPI containing a blend of albuterol sulfate and alpha-lactose monohydrate. The inhaler contains 200 actuations, each delivering 90 mcg of albuterol base ex-mouthpiece; the inhaler is equipped with a dose counter that shows 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. Teva has developed the eModule as part of a system to assist a patient with asthma to appropriately use the eMDPI inhaler. The system is described in more practical terms as an inhaler with an integrated data logger capable of storing and transmitting timestamped data to support the data logging functionality.

The on-board electronics and power source are fully integrated into the eMDPI and are designed to operate for the life of the inhaler without intervention, ie, the battery does not require replacement or recharging.

The addition of the required electronics has no impact on the pharmaceutical performance of the inhaler or on the required user steps to take a dose. A schematic of the inhaler with the additional eModule is shown in Figure 3.

Figure 3: Current Inhaler (Left) Versus Inhaler with Additional Electronics Module (Right)



Additional details may be found in Table 4 and in the IB.

The information from the eModule may be transmitted wirelessly (Bluetooth Low Energy) to an App. From the App, data may be transmitted to the DHP, which consists of a Cloud solution, and then to a dashboard. This allows the patient and/or the caregiver to track when and how well the inhaler was used.

By consenting to enroll in the study, the patient must also download the smart device App (with the assistance of investigational center personnel), accept the smart device App's Privacy Notice and Terms of Use, and also agree to share his/her data to a provider-facing dashboard utilized by the iHCP and investigational center study team. An ICF will be provided to the patients which will elaborate, among other ways, Teva's ways of use and storing of patient data collected through the smart device App. The patient will be entering into a direct contractual relationship with Teva which will govern, among other things, Teva's rights to use and store patient data collected through the smart device App. If the patient does not accept the smart device App's Privacy Notice and Terms of Use and does not also agree to share their data to the provider-facing dashboard utilized by the iHCP and investigational center study team, then the patient cannot enroll in the study. At the end of treatment/ET visit (Visit 2), investigational center personnel will remove the App from the patient's smart device.

5.1.1.1. Starting Dose and Dose Levels

The prescribed dose will be 90 mcg, 1 to 2 inhalations every 4 to 6 hours, as needed. No dose escalations are planned.

5.1.1.2. Dose Modification and Dose Stratification

Not applicable.

5.1.2. Medical Devices

Instructions for medical device use are provided in the Study Pharmacy Manual.

5.1.2.1. Application

The software App is a customer facing software/focused smart device application for patients using the Albuterol eMDPI Inhalation Powder combination product. The intention of the smart device App is to engage patients with asthma and/or COPD (and their caregivers) by tracking medication usage, raising awareness of medication use patterns, allowing users to self-assess their respiratory symptoms on a daily basis, sharing information on local environmental conditions, and producing user reports to review their data over time.

The software consists of a smart device application compatible for iPhone operating systems (iOS) and Android operating systems that will store data locally on the patient's smart device. The App will receive a patient's inhaler use/event data automatically from the inhaler devices via Bluetooth on a smart device. The smart device camera will be used for scanning and pairing. This data will allow the patient to track their usage of medication, inhalation results, and self-assessments related to their asthma and/or COPD. The App gets environment information for the specific location of the patient.

5.1.2.2. Teva Digital Health Platform (Cloud Solution)

The Teva DHP is a system that stores and transfers inhaler use/event data collected from the App. The Cloud solution automatically synchronizes with the App after events and/or at predetermined time periods/intervals. An internet connection to the smart device (eg, wireless or cellular phone network) is required in order for communication to be established between the App and the Cloud solution. The Cloud solution will not send any notifications to the App. The Cloud solution does not create, modify, or delete patient information.

Patient privacy will be maintained according to the laws and regulations, and patient identifiers will be substituted to maintain a patient's privacy to reviewers of the data.

5.1.2.3. Dashboard

The DHP may be used to provide patient-specific data to the iHCP via the dashboard, a secure web interface. The data available on the dashboard are the inhaler use data and patient self-assessments from the App. The patient has no interaction with the dashboard. Teva personnel will have no access to the dashboard.

5.1.3. Reference Investigational Medicinal Product or Device

Not applicable.

5.1.4. Placebo Investigational Medicinal Product or Device

Not applicable.

Table 4: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP	Reference IMP
Trade name	Albuterol eMDPI	None	None
Formulation	Oral inhalation powder	NA	NA
Unit dose strength	117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base) from the device reservoir to provide a delivered dose of 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base)	NA	NA
Route of administration	Oral inhalation	NA	NA
Dosing instructions	1 to 2 oral inhalations every 4 to 6 hours, as needed	NA	NA
Packaging	NA	NA	NA
Manufacturer	Teva Pharmaceutical Industries, Ltd. Jerusalem, Israel, or Teva Pharmaceuticals Ireland, Waterford, Ireland	NA	NA

eMDPI=multidose dry powder inhaler with integrated electronic module; IMP=investigational medicinal product; NA=not applicable.

5.2. Preparation, Handling, Labeling, Storage, and Accountability for IMPs

5.2.1. Storage and Security

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

The IMP must be stored at room temperature (15°C to 25°C [59°F to 77°F]) and not exposed to extreme heat, cold, or humidity. The investigational center personnel are responsible for acknowledging receipt of the IMP using a Randomization and Trial Supply Management (RTSM) system.

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 and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMP 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 national and local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive IMP, and only authorized personnel at the investigational center may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized personnel at the investigational center. 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 end of treatment (Visit 2) or at the ET visit.

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 investigational center 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. All empty, partially used, and unused inhalers will be collected at the end of the study and will be returned to the sponsor or designee per sponsor instructions.

Further guidance and information are provided in the Study Pharmacy Manual.

5.3. Justification for Investigational Medicinal Product

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The prescribed dose of Albuterol eMDPI (now US FDA approved as PROAIR DIGIHALER) used in this study (ie, 90 mcg, 1 to 2 inhalations every 4 to 6 hours, as needed) was selected based on the prescribing information for PROAIR DIGIHALER.

PROAIR DIGIHALER 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 EIB. For the relief of acute asthma symptoms, PROAIR DIGIHALER is recommended at a dosage of 2 inhalations (ie, 180 mcg of albuterol base ex-mouthpiece) repeated every 4 to 6 hours, as needed. 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 DIGIHALER 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 DIGIHALER 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 are advised to consult with their primary physician for treatment.

5.5. Restrictions

There are no additional restrictions beyond the inclusion and exclusion criteria in this study and the prohibited medication noted in Section 5.6.

5.6. Prior and Concomitant Medication or Therapy

Any concomitant medication a patient is taking at screening and up to the final visit 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 (WHO) drug dictionary (WHO Drug).

The use of other SABA products, by the DS group, is prohibited during this study except for the use of nebulized albuterol, as needed, in the ED for an acute exacerbation of asthma.

At the end of treatment visit (Visit 2), 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 the final visit.

5.7. Procedures for Monitoring Patient Compliance

Since the IMP is a rescue medication, it will be used on an “as needed” basis. The investigator will be responsible for dispensing IMP, training patients on the correct use of IMP, return of IMP, 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 patients will be randomly assigned to the DS group or CC group in a 1:1 ratio stratified by investigational center, using a RTSM system. Since this an open-label study, blinding is not applicable.

5.9. Data Monitoring Committee

There will be no Data Monitoring Committee for this study.

6. ASSESSMENT OF EFFICACY

The efficacy of the drug product will not be evaluated in this study. The focus of this study is the engagement of the patient with the Albuterol eMDPI DS.

6.1. Assessments of Patient-Reported Outcomes

6.1.1. Asthma Control Test

The ACT is a simple, patient-completed tool used for the assessment of overall asthma control. The 5 items included in the ACT assess daytime and nighttime asthma symptoms, use of rescue medication, and impact of asthma on daily functioning. Each item in the ACT is scored on a 5-point scale, with summation of all items providing scores ranging from 5 to 25. The scores span the continuum of poor control of asthma (score of 5) to complete control of asthma (score of 25), with a cutoff score of 19 and below indicating patients with poorly controlled asthma (Schatz et al 2006).

The ACT should be the first questionnaire completed by all patients during a study visit (the second should be the BMQ, and the third the BIPQ (both by patients 18 years of age or older), and should precede any discussion between the patient and investigational center personnel. The self-administered version of the ACT will be answered by the patients at the investigational center at Visit 1, Visit 2, or at the Early Termination (ET) visit. The investigators and personnel will be provided with detailed instructions for administering the ACT in order to achieve maximum compliance in a clinical study environment and maximum data quality. Caregivers or investigational center personnel will not be allowed to interfere or communicate with the patient completing the questionnaire beyond restating the question(s) on the questionnaire exactly as they have been written. After completion of the ACT, investigational center personnel will check the questionnaires for completeness and legibility. Detailed instructions for administering, scoring, and analyzing the ACT are provided in the Statistical Analysis Plan.

6.1.2. Beliefs about Medicines Questionnaire

The BMQ is used to assess cognitive representations of medicine (Horne, Weinman, and Hankins 1999). The BMQ-Specific (BMQ-S11) is an 11-item questionnaire that assesses representation of medication prescribed for personal use and the BMQ-General assesses beliefs about medicines in general. For the purposes of this study, the BMQ-S11 will be completed by patients, 18 years of age or older, at the investigational center at Visit 1, Visit 2, or at the ET visit. The BMQ should be the second questionnaire completed during a study visit following the ACT.

6.1.3. Brief Illness Perception Questionnaire

The BIPQ is a 9-item questionnaire designed to rapidly assess cognitive and emotional representations of illness (Broadbent et al 2006). The BIPQ uses a single-item scale approach to assess perception on a 0-10 response scale. It is developed by forming one question that best summarizes the items contained in each subscale of the Illness Perception Questionnaire-Revised which has over 80 items. The BIPQ comprises 5 items on cognitive representation of illness perception: consequences, timeline, personal control, treatment control, and identity. There are 2 items on emotional representation: concern and emotions; one item is on illness

comprehensibility. The last item is on perceived cause of illness, in which respondents list the 3 most important causal factors in their illness. For this questionnaire, the general word 'illness' can be replaced by the name of a particular illness such as asthma. The word 'treatment' in the treatment control item can be replaced by a particular treatment such as 'surgery' or 'physiotherapy' (Broadbent et al 2006). The discriminant validity of the questionnaire is supported by its ability to distinguish between different illnesses, namely asthma, diabetes, colds, myocardial infarct prior to discharge, and pre-diagnosis chest pain patients waiting stress exercise testing. The BIPQ will be answered by the patients, 18 years of age or older, at the investigational center at Visit 1, Visit 2, or at the ET visit. The BIPQ should be the third questionnaire completed during a study visit following the BMQ.

6.1.4. System Usability Questionnaire

The SUS will be used to explore device acceptability and usability for patients in the DS group. It is a 10-question tool that provides a composite measure of the overall usability of the system being studied. It has been used extensively across many industries, patient types, and technologies, and has been used in studies of patients with asthma and COPD (Brooke 1996). The SUS will be answered by patients in the DS group, 18 years of age or older, at Visit 2, or at the ET visit. The SUS will be completed after all other questionnaires.

An SUS regarding the use of the dashboard will be completed by investigational center personnel at the end of the study.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, adverse device effects, vital signs measurements, and use of concomitant medications.

Adverse events are categorized by ICH guidelines, and adverse device effects are categorized and classified according to International Organization for Standardization (ISO) standard 14155:2011(E).

Device deficiencies that are not associated with an adverse event as well as those that have the potential to cause a serious adverse event are covered in Appendix F.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients or clinical investigation subjects, users or other persons, whether or not related (causal relationship) to the pharmaceutical product (treatment), investigational medical device, or comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

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. 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 medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug/drug, drug/device, or device/device interactions
- events occurring during diagnostic procedures of this study

Worsening of asthma that occurs during the study that is not typical of the patient's daily symptoms or leads to the patient's discontinuation will be considered an adverse event.

A CAE will be defined by 1 of the following: 1) in-patient hospitalization because of asthma, 2) emergency treatment because of asthma, 3) a worsening of asthma symptoms leading to the use of prednisone or systemic corticosteroids for 3 days or more, or 4) a reduction in FEV_1 of 20% or greater. Patients will be instructed to contact the study investigational center in the event of a CAE.

All CAE events require documentation by the investigator in the CAE Page in the CRF, as well as in the adverse event CRF. All evaluations entered into the CAE Page require the investigational center to obtain source documentation of all CAEs that occur during the treatment period to confirm the accuracy of the information obtained from the patient. Any CAE that meets serious adverse event criteria will be reported as a serious adverse event (Section 7.1.5.1).

7.1.2. Recording and Reporting of Adverse Events

For recording of an adverse event, the study period is defined for each patient as the time period from signature of the ICF to the end of the follow-up period (end of study [follow-up telephone call]). The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered and until the end of the follow-up period.

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 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 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 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 1 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 Investigational Medicinal Product

The relationship of an adverse event to the IMP is characterized as follows (Table 5):

Table 5: The Relationship of an Adverse Event to the Investigational Medicinal Product

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.

IMP=investigational medicinal product.

7.1.5. Serious Adverse Events

For recording of a serious adverse event, the study period is defined for each patient as that time period from signature of the ICF to the end of the follow-up period. Serious adverse events occurring in a patient after the end of the follow-up period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

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 a 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 1 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 for this study is the IB.

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 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 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 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 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/MedWatch form/Extensible Markup Language file to the LSO/CRO for submission to the competent authorities, Independent Ethics Committee/Institutional Review Board (IEC/IRB), 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 IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of Albuterol 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 Albuterol eMDPI

7.1.6. Protocol-Defined Adverse Events of Special Interest

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

7.1.7. 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. Adverse Device Effects

An adverse device effect is an adverse event related to the use of an investigational medical device or a combination product. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device, including any event resulting from user error or from intentional misuse of the investigational medical device.

7.2.1. Adverse Device Effect Reporting

Adverse device effects (Figure 4) must be recorded on both the source documentation and the CRF.

All adverse device effects shall be reviewed by the investigator, the medical monitor, and the sponsor. The investigator and sponsor will record all relevant information regarding every adverse device effect/serious adverse device effect and device deficiency and will categorize each as guided in Section 7.2.

The investigator should make an initial determination whether the adverse event may be related to a device deficiency.

Adverse device effects and device deficiencies will be listed in the clinical study report (CSR).

7.2.2. Serious Adverse Device Effects

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (Section 7.1.5.1).

An unanticipated serious adverse device effect is a serious adverse device effect that, by its nature, incidence, severity, or outcome, has not been listed in Appendix F (Appendix Table 1 and Appendix Table 2).

7.2.2.1. Serious Adverse Device Effect Reporting

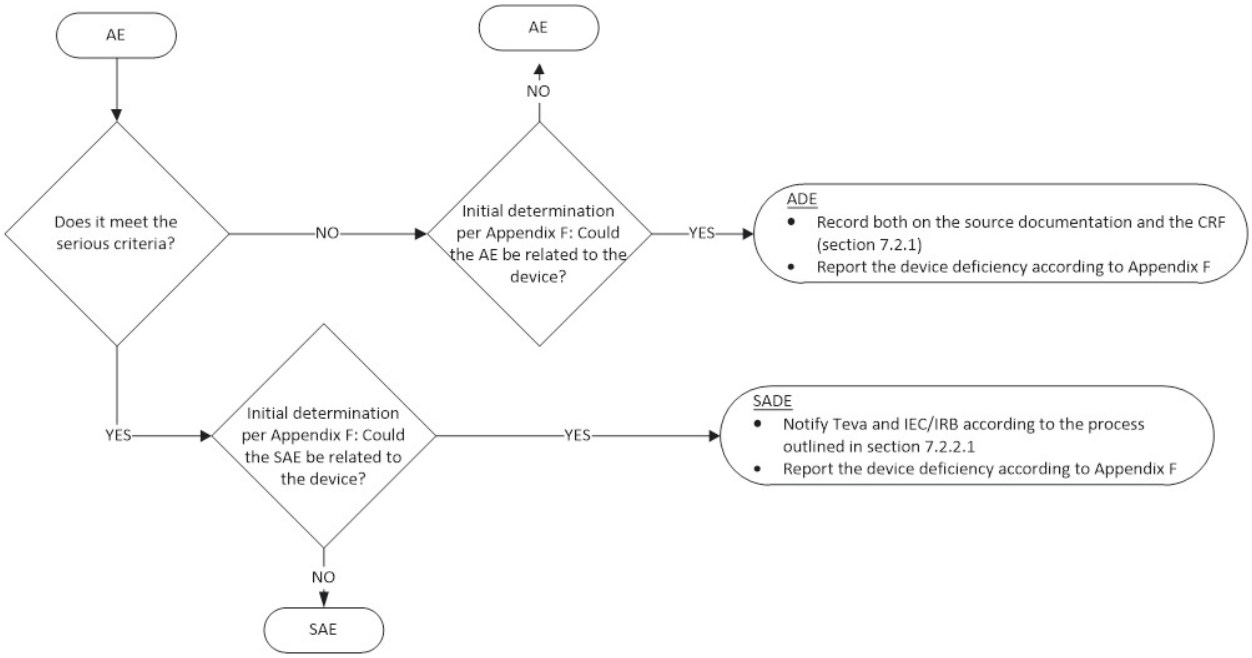
The investigator will report to the sponsor, without unjustified delay, all serious adverse device effects (within 24 hours); this information shall be promptly followed by detailed written reports as described below.

The process and contact details for serious adverse device effect reporting are the same as for serious adverse event reporting provided in Section 7.1.5.3.

Events shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor using the appropriate form according to national and local regulations.

The investigator should use Appendix F (Appendix Table 1 and Appendix Table 2) to make an initial determination whether the serious adverse event may be related to a device deficiency.

Figure 4: Decision Tree for Adverse Events and Adverse Device Effects Classification



AE=adverse event; ADE=adverse device effect; CRF=case report form; IEC=Independent Ethics Committee; IRB=Institutional Review Board; SADE=serious adverse device effect; SAE=serious adverse event.

7.3. Pregnancy

All pregnancies of women participating in the study, that occur during the study, or within at least 5 half-lives or 30 days for unknown 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 participating in the study 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.

Since there is no evidence of teratogenicity, genotoxicity, fetotoxicity, or spermatotoxicity for this IMP, female partners will not be required to sign an ICF to monitor the outcome of the pregnancy.

If the pregnancy in the woman participating in the study does not continue to term, 1 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.

7.4. Medication Error and Special Situations Related to the Investigational Medicinal Product

Any administration of IMP that is not in accordance with the study protocol should be reported in the patient's source documents (Appendix C), regardless of whether or not an adverse event occurs as a result.

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 or reference 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. Occupational exposure: Exposure to an IMP as a result of one's professional or nonprofessional occupation.

7.5. Clinical Laboratory Tests

No clinical laboratory tests are scheduled to be performed during this study.

7.6. Physical Examinations

No physical examinations are scheduled to be performed during this study.

7.7. Vital Signs

Vital signs (blood pressure [systolic/diastolic], pulse rate, and respiratory rate) will be measured at the time points detailed in Table 3. All vital signs results outside of the reference ranges will be judged by the investigator as belonging to 1 of the following categories:

- abnormal and not clinically significant

- abnormal and clinically significant

Before blood pressure and pulse are measured, the patient must rest in a seated position for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital sign value, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2.

In addition, potentially clinically significant values will be predefined by the sponsor for selected vital sign parameters and will be detailed in the Statistical Analysis Plan.

7.8. Electrocardiography

No electrocardiogram measurements are scheduled to be performed during 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 in the CSR.

9.1. Sample Size and Power Considerations

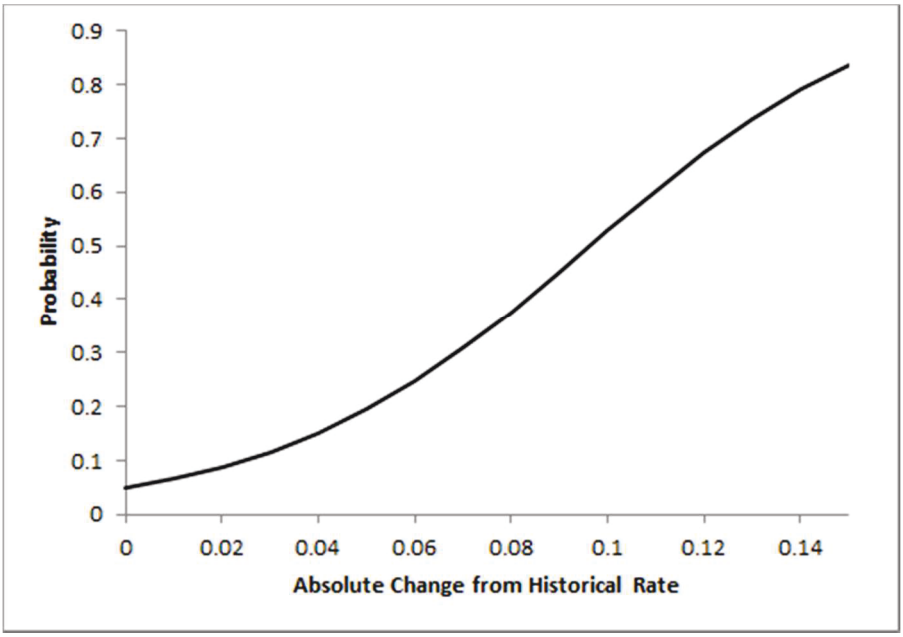
Sample size estimates are based upon the assumption that the absolute differences between the DS and CC groups and the associated operational characteristics will be similar to the absolute differences and operational characteristics of the DS and CC groups noted in the sample size rationale for the study design.

The recommended sample size for the study is 150 evaluable patients per group (30 investigational centers with each investigational center enrolling at least 10 patients), 300 patients in total. Accounting for a dropout rate of 10%, this leads to a recommended total number of 330 enrolled patients.

With this sample size and assuming a true absolute difference in proportions (treatment effect as the estimated response rate for the CC group is 60% and for the DS group is 73%) between the groups of at least 13%, the probability that the posterior probability will be at least 95% is 0.77 (power) (analogous to 1-sided p-value < 0.05) (Merchant et al 2016). Assuming no treatment effect (difference in proportions between the groups is 0%, ie, Type 1 error) then the probability is 0.05 that posterior probability will be at least 95% is 0.05.

It should be noted that both power and Type 1 error are dependent on the absolute difference between the DS and the CC groups as illustrated in Figure 5 below by the operational characteristics calculated for the study design:

Figure 5: Operational Characteristics Calculated for the Study Design



9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients. In the intent-to-treat (ITT) analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. This analysis population will be used for summarization of patient disposition and demographic and baseline characteristics, as appropriate.

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 including only patients who receive at least 1 dose of IMP (IMP is albuterol eMDPI for the DS group and standard-of-care albuterol-administering rescue medication for the CC group) and at least 1 postbaseline assessment on any of the study endpoints (primary, secondary, or exploratory).

In the mITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. This analysis will be used for all primary, secondary, and exploratory endpoint analyses.

9.2.3. Safety Analysis Set

This analysis set will include all patients in the DS group who receive at least 1 dose of IMP and all patients in the CC group. In the safety analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified. This analysis set will be used for all safety analyses.

Additional analyses sets may be defined in the Statistical Analysis Plan, if appropriate.

9.3. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses, ie, there is no plan to estimate (impute) missing data, unless otherwise specified in the Statistical Analysis Plan.

9.3.1. Handling Withdrawals and Missing Data

For the primary endpoint, missing data will not be imputed, unless otherwise specified in the Statistical Analysis Plan.

9.4. Study Population

The ITT Analysis Set (Section 9.2.1) will be used for all study population summaries noted below, unless otherwise specified. Summaries will be presented for all patients.

9.4.1. Patient Disposition

Data from patients screened; patients screened but not randomized and reason for not being randomized; patients in the ITT analysis set; patients in the ITT analysis set who did not attempt to download the App; patients in the ITT analysis set who did not use the inhaler; patients in the mITT and safety analysis sets; patients who completed the study; and patients who withdrew

from the study and the reason for withdrawal will be summarized using descriptive summary statistics (number, %).

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, current medication at screening/baseline, and treatment history related to asthma, 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. Analyses

9.5.1. Primary Endpoint

The primary endpoint is the proportion of patients reaching well-controlled asthma as defined by an ACT score of greater than or equal to 20 or a clinically important improvement in asthma control as defined by an increase of at least 3 units on the ACT score from baseline at the end of the 12-week treatment period (responder analysis of DS versus CC group with responders defined by an ACT score of greater than or equal to 20 or an increase by greater than or equal to 3 units on the ACT score).

9.5.2. Secondary Endpoints

Secondary endpoint #1 is the frequency and types of interventions done to improve asthma control including:

- number of discussions between patient and iHCP regarding inhaler technique or adherence
- number of adjustments of therapy including:
    - increased or decreased doses of inhaled medication
    - change to different inhaled medication
    - additional inhaled medication
    - addition of a systemic corticosteroid medication for asthma or another controller, including a LAMA or biologics
- frequency of intervention to manage comorbid conditions associated with poor asthma control GERD, sinusitis, etc.)

Secondary endpoint #2 is the change from baseline in the mean weekly SABA usage and the change from baseline in the number of SABA-free days over the 12-week treatment period for the DS group.

Secondary endpoint #3 is the assessment of the DS (eMDPI, App and dashboard) acceptability and usability, utilizing the SUS, completed by the patients in the DS group, 18 years of age or older, and investigational center personnel at the end of the study.

Secondary endpoint #4 is the assessment of patients' beliefs and perceptions about their disease and treatment, utilizing the BMQ and the BIPQ for both the DS and CC groups, patients 18 years of age or older, describing their behavioral profile at baseline and at the end of the study.

9.5.3. Exploratory/Other Endpoints

The exploratory endpoints are:

9.5.4. Planned Method of Analysis

9.5.4.1. Primary Analysis

To analyze the primary variable, the following estimand framework will be used:

1. 1. Analysis will be performed on the mITT set.
2. A binary distribution is assumed for the primary endpoint. Patients who discontinue early due to technology failure, disliking the digital platform, disease worsening, adverse experience or disliking the IMP will be counted as treatment failures For those who discontinue early not due to these reasons, the ACT value assessed at the ET visit will be used.
3. Summary measure: A successful differentiation between the 2 groups will be determined by a Bayesian posterior probability for $\beta_1 > 0$ greater than 0.95 (1-sided). The following statistical methods will be utilized:

Logistic regression model allowing for different response rates at enrolling investigational centers will be used for testing the hypothesis $H_0: \beta_1 = 0$, $H_1: \beta_1 > 0$ in the following model:

$$ln\frac{p_{ij}}{1-p_{ij}} = \delta_j + \beta_0 baseline\ ACT\ value + \beta_1 x_{ij}$$

where i = treatment group, j = investigational center, x_{ij} = treatment group i for investigational center j, p_{ij} = response proportion of treatment group i in investigational center j.

Non-informative priors will be assumed for all coefficients.

Estimates of odds ratio and individual proportions with corresponding credible intervals will be presented.

9.5.4.2. Sensitivity Analysis

If appropriate, sensitivity analyses will be specified in the Statistical Analysis Plan.

9.5.4.3. Secondary Analysis

All summaries of all secondary endpoints will be based on the mITT analysis set and analyzed descriptively.

For continuous variables, descriptive statistics (number [n], mean, standard deviation, median, minimum, and maximum) will be provided for observed values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

9.5.4.4. Other Analyses

No other analyses are planned.

9.5.4.5. Exploratory Analysis

[redacted]

9.6. Multiple Comparisons and Multiplicity

Since there is only 1 primary endpoint and the multiple secondary endpoints will be analyzed using descriptive statistical analysis techniques, no adjustments for multiple comparisons/multiplicity will be made for the preplanned multiple comparisons/endpoints.

9.7. Safety Analysis

Safety analyses will be performed using the safety analysis set. For categorical variables, patient counts and percentages will be provided.

Safety assessments and time points are provided in Table 3.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or System Organ Class (SOC) category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility; defined as related or with missing relationship [Section 7.1.4]; overall; and by severity), serious adverse events, adverse events causing withdrawal from the study, and adverse device effects. Summaries will be presented by treatment group and for all patients. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

Changes in vital signs measurements data will be summarized descriptively. All values will be compared with predefined criteria to identify potentially clinically significant values or changes, and such values will be listed.

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

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be provided for observed 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, adverse device effects, and potentially clinically significant abnormal values (vital signs) 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 is not applicable to this study.

9.9. Planned Interim Analysis

No interim analyses are planned.

9.10. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in any 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.

Refer to Appendix F for the definition of a clinical product complaint or device deficiency and investigator responsibilities in the management of a clinical product complaint or device deficiency.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [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 IMP 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 Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with competent authorities.

See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IEC and 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 information on direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

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.

The 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, eg, 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 H for information regarding the publication policy.

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 04 Dated 12 March 2021

The primary reason for this amendment is to add an exclusion criterion to preclude patients with previous exposure to the Digihaler device from participating in the study. This amendment is considered to be substantial (ie, requires approval by CA, IEC, and/or IRB) by the sponsor's Authorized Representative. 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.

Minor editorial changes (typos, punctuation, replacing text with abbreviations, etc) have been made to the protocol and protocol synopsis, as appropriate.

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Section 2.1 Primary and Secondary Study Objectives and Endpoints		
This secondary endpoint ~~will describe~~ is the frequency and types of interventions done to improve asthma control including:	This secondary endpoint is the frequency and types of interventions done to improve asthma control including:	Clarified phrasing.
Section 3.1 Introduction		
The study will consist of a screening/baseline visit (Visit 1), a 12-week open-label treatment period with Visit 2, and a follow-up telephone call (2 weeks following treatment completion.	The study will consist of a screening/baseline visit (Visit 1), a 12-week open-label treatment period with Visit 2, and a follow-up telephone call (2 weeks following treatment completion.	Revised for clarity and specificity.
All patients will have a screening/baseline visit (Visit 1), at which they will be asked if they use a smart device and use different applications on their smart devices.	All patients will have a screening/baseline visit (Visit 1), at which they will be asked if they use a smart device and use different applications on their smart devices.	Revised for clarity and specificity.
For all patients, at Visit 2 and at each Clinically Driven Assessment, if necessary, the iHCP will record answers to Asthma Management questions ~~regarding what interventions occurred as a consequence of the Clinically Driven Assessment~~, including discussions regarding adherence, or inhaler technique, treatment adjustments, or additions of new treatments, including biologic medication usage. Additionally, in the case of a Clinically Driven Assessment (for patients in the DS group), the iHCP will be asked whether or not the contact with the	For all patients, at Visit 2 and at each Clinically Driven Assessment, if necessary, the iHCP will record answers to Asthma Management questions, including discussions regarding adherence, or inhaler technique, treatment adjustments, or additions of new treatments, including biologic medication usage. Additionally, in the case of a Clinically Driven Assessment (for patients in the DS group), the iHCP will be asked whether or not	Clarified phrasing.

Original text with changes shown	New wording	Reason/Justification for change
patient was originated from the iHCP interaction with the dashboard.	the contact with the patient was originated from the iHCP interaction with the dashboard.	
Section 4.1 Patient Inclusion Criteria		
f. [Revision 1] The patient can read and communicate in English and is familiar with and is willing to use his/her own smart device that meets the minimum App requirements and download and use the App.	f. [Revision 1] The patient can read and communicate in English and is familiar with and is willing to use his/her own smart device that meets the minimum App requirements and download and use the App.	Revised for clarity and specificity.
Section 4.2 Patient Exclusion Criteria		
g. [Revision 1] The patient has any treatment with biologics for asthma (eg, omalizumab, anti-interleukin (IL) 5, anti-IL5R, anti-IL4R), or has had such treatment within the last 90 days. (However, during the study, patients can be escalated to therapy with such agents if clinically indicated in the judgment of the investigator as part of their asthma management and remain in the study.)	[Revision 1] The patient has any treatment with biologics for asthma (eg, omalizumab, anti-interleukin (IL) 5, anti-IL5R, anti-IL4R), or has had such treatment within the last 90 days. (However, during the study, patients can be escalated to therapy with such agents if clinically indicated in the judgment of the investigator as part of their asthma management and remain in the study.)	Clarified escalation of biological therapy for asthma is permitted during the study if clinically required for disease management.
i. [New criterion] The patient is currently being treated prior to enrollment with a digital inhaler system, including the Digihaler system or an external "bolt on" digital system designed to monitor inhaler usage, such as the Propeller Health or Adherium systems.	i. [New criterion] The patient has previously participated in a Digihaler study or is currently being treated prior to enrollment with a digital inhaler system, including the Digihaler system or an external "bolt on" digital system designed to monitor inhaler usage, such as the Propeller Health or Adherium systems.	Added an additional exclusion criterion.
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~~end of treatment (Visit 2) or at the ET visit~~early termination~~.	Patients will be instructed to return all IMP (empty, partially used, and unused inhalers) to the investigational center at end of treatment (Visit 2) or at the ET visit.	Revised for clarity and specificity.
Section 6.1.4 System Usability Questionnaire		
An SUS regarding the use of the dashboard will be completed by investigational center personnel~~, regarding the use of the dashboard,~~ at the end of the study.	An SUS regarding the use of the dashboard will be completed by investigational center personnel at the end of the study.	Revised for clarity.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.4 Medication Error and Special Situations Related to the Investigational Medicinal Product.		
~~6.Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.~~	Text was deleted.	Removed breastfeeding as a special situation related to IMP since there are no exclusions/special provisions listed in the protocol or package insert in regards to pregnancy, women of childbearing potential, or breastfeeding.
Section 9.5.2 Secondary Endpoints		
Secondary endpoint #1 ~~will describe~~is the frequency and types of interventions done to improve asthma control including:	Secondary endpoint #1 is the frequency and types of interventions done to improve asthma control including:	Clarified phrasing.
Appendix C QUALITY CONTROL AND QUALITY ASSURANCE		
Study Monitoring In case of an emergency situation (eg, the COVID-19 pandemic), where study monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with local regulations.	**Study Monitoring** In case of an emergency situation (eg, the COVID-19 pandemic), where study monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with local regulations.	Clarified that remote monitoring is permitted in case of an emergency situation.
Audit and Inspection In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with local regulations.	**Audit and Inspection** In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with local regulations.	Clarified that remote audits and inspections are permitted in case of an emergency situation.

16.2. Amendment 03 Dated 30 July 2020

The primary reason for this amendment is to clarify the definitions of the analysis sets. 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. All major changes to the protocol body are listed below in the table, and are reflected in the synopsis, as applicable. Minor editorial changes (typos, punctuation, etc) have been made to the protocol (and protocol synopsis, as appropriate).

Table 3 (Study Procedures and Assessments) and the synopsis have been revised to reflect the changes below.

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Title page		
Sponsor Teva Branded Pharmaceutical Products R&D, Inc. ~~41 Moores Road~~ 145 Brandywine Parkway ~~Frazer, Pennsylvania 19355~~ West Chester, PA 19380 United States of America	Sponsor Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, PA 19380 United States of America	Revised to reflect new sponsor address.
© 2020 ~~2019~~ Teva Branded Pharmaceutical Products R&D, Inc.	© 2020 Teva Branded Pharmaceutical Products R&D, Inc.	Revised with correct year.
Section 1.1 Introduction		
As the recommended drug for relief of acute asthmatic symptoms and as the prophylaxis for exercise-induced bronchoconstriction, short-acting beta$_2$ agonists (SABAs), such as albuterol, are a mainstay of asthma management. Albuterol sulfate 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 (albuterol sulfate) RESPICLICK® Inhalation Powder is available in the United States (US) 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).~~ … To eliminate the necessity for coordinating actuation with inspiration, Teva ~~has~~ developed the breath-actuated inhaler PROAIR® RESPICLICK®, which utilizes a formulation blend of albuterol sulfate with lactose as an excipient…. ~~Albuterol sulfate 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 US since March of 2015~~. ~~On 21 December 2018, the US FDA approved Albuterol eMDPI as~~ PROAIR RESPICLICK® ~~DIGIHALER~~™ (albuterol sulfate inhalation powder) has been available in the United States (US) since	As the recommended drug for relief of acute asthmatic symptoms and as the prophylaxis for exercise-induced bronchoconstriction, short-acting beta$_2$ agonists (SABAs), such as albuterol, are a mainstay of asthma management. Albuterol sulfate 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]…. ....To eliminate the necessity for coordinating actuation with inspiration, Teva developed the breath-actuated inhaler PROAIR® RESPICLICK®, which utilizes a formulation blend of albuterol sulfate with lactose as an excipient…. PROAIR RESPICLICK (albuterol sulfate inhalation powder) has been available in the United States (US) since March 2015. It is indicated for treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm in patients 4 years of age and older. On 21 December 2018, the US FDA approved Albuterol multidose dry powder inhaler	Reorganized the section to better explain the relationship between PROAIR DIGIHALER and PROAIR RESPICLICK, as FDA-approved labeling is now available for DIGIHALER that was not available at the time of Amendment 02.

Original text with changes shown	New wording	Reason/Justification for change
March 2015. It is indicated~~), 90 mcg of albuterol base per actuation,~~ for treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm in patients 4 years of age and older. On 21 December 2018, the US FDA approved Albuterol multidose dry powder inhaler (MDPI) with an integrated electronic module (eMDPI) as PROAIR® DIGIHALER™ (albuterol sulfate inhalation powder), 90 mcg of albuterol base per actuation, for the same indication as PROAIR RESPICLICK. PROAIR DIGIHALER contains a built-in electronic module (eModule; ie, the Digihaler) that detects, records, and stores data on inhaler events for transmission to a mobile application (App). More detailed prescribing information for this product may be found in the Investigator's Brochure (IB). In this study, 90 mcg of albuterol sulfate is delivered via PROAIR DIGIHALER.	(MDPI) with an integrated electronic module (eMDPI) as PROAIR® DIGIHALER™ (albuterol sulfate inhalation powder), 90 mcg of albuterol base per actuation, for the same indication as PROAIR RESPICLICK. PROAIR DIGIHALER contains a built-in electronic module (eModule; ie, the Digihaler) that detects, records, and stores data on inhaler events for transmission to a mobile application (App). More detailed prescribing information for this product may be found in the Investigator's Brochure (IB). In this study, 90 mcg of albuterol sulfate is delivered via PROAIR DIGIHALER….	
The purpose of the study is to evaluate whether outcomes for patients using the Albuterol eMDPI DS can be optimized ~~outcomes~~ better than a concurrent control (CC) group who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period.	The purpose of the study is to evaluate whether outcomes for patients using the Albuterol eMDPI DS can be optimized better than a concurrent control (CC) group who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period.	Clarified phrasing.
Section 1.2 Findings from Nonclinical and Clinical Studies		
~~In the clinical development program for PROAIR RESPICLICK, the IMP was reported using nomenclature other than that of the then-unbranded product. In the descriptions of the PROAIR RESPICLICK studies in 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 the clinical studies are provided in this section. Bronchospasm Associated with Asthma: In two 12-week, randomized, double-blind, placebo-controlled studies of identical design (Study 1 and Study 2), albuterol sulfate MDPI (153 patients)~~PROAIR~~	Brief summaries of the clinical studies are provided in this section. Bronchospasm Associated with Asthma: In two 12-week, randomized, double-blind, placebo-controlled studies of identical design (Study 1 and Study 2), albuterol sulfate MDPI (153 patients) was compared to a matched placebo dry powder inhaler (163 patients) in asthmatic patients 12 to 76 years of age at a dose of 180 mcg albuterol 4 times daily…. Serial measurements of forced expiratory volume in 1	Updated text to more closely match the DIGIHALER labeling, which was not available at the time of Amendment 02.

Original text with changes shown	New wording	Reason/Justification for change
~~RESPICLICK~~ was compared to a matched placebo dry powder inhaler ~~(~~in ~~153 and~~ 163 patients) in asthmatic patients ~~with asthma, respectively,~~ 12 to 76 years of age at a dose of 180 mcg albuterol 4 times daily…. Serial measurements of forced expiratory volume in 1 second (FEV_1) demonstrated that 2 inhalations of albuterol sulfate MDPI~~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. Consistent results were observed in~~Results of~~ Study 2. ~~were consistent with those of Study 1~~. In a double-blind, randomized, placebo-controlled, single-dose, crossover study evaluating albuterol sulfate MDPI~~PROAIR RESPICLICK~~ and PROAIR® HFA in 71 adult and adolescent patients 12 years of age and older with persistent asthma, albuterol sulfate MDPI~~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 albuterol sulfate MDPI~~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 when they~~who~~ received placebo…. … Clinical Safety: A total of 1289 subjects were treated with albuterol sulfate MDPI~~PROAIR RESPICLICK~~ during the clinical development program…. In a long-term study of 168 patients treated with albuterol sulfate MDPI~~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.	second (FEV_1) demonstrated that 2 inhalations of albuterol sulfate MDPI 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. Consistent results were observed in Study 2. In a double-blind, randomized, placebo-controlled, single-dose, crossover study evaluating albuterol sulfate MDPI and PROAIR® HFA in 71 adult and adolescent patients 12 years of age and older with persistent asthma, albuterol sulfate MDPI 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 albuterol sulfate MDPI 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 when they received placebo.... … Clinical Safety: A total of 1289 subjects were treated with albuterol sulfate MDPI during the clinical development program…. In a long-term study of 168 patients treated with albuterol sulfate MDPI 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	

Original text with changes shown	New wording	Reason/Justification for change
In a small cumulative dose study, tremor, palpitations, and headache were the most frequently occurring (≥5%) adverse events.	small cumulative dose study, tremor, palpitations, and headache were the most frequently occurring (≥5%) adverse events.	
Section 1.3.1 Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)		
This open-label study is being undertaken to evaluate whether outcomes for patients using the Albuterol eMDPI DS can be optimized ~~outcomes~~ better than a CC group who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period.	This open-label study is being undertaken to evaluate whether outcomes for patients using the Albuterol eMDPI DS can be optimized better than a CC group who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period.	Clarified phrasing.
… ~~Furthermore, the steps to take a dose of the Albuterol 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….~~	Text was deleted	Removed context of RESPICLICK, since approved USPI for DIGIHALER is now available.
Section 2.1 Primary and Secondary Study Objectives and Endpoints		
o addition of ~~an oral or parenteral~~ a systemic corticosteroid medication for asthma or another controller, including a long-acting muscarinic antagonist (LAMA) or biologics	o addition of a systemic corticosteroid medication for asthma or another controller, including a long-acting muscarinic antagonist (LAMA) or biologics	Revised for clarity and specificity.
Section 2.2 Exploratory Objectives and Endpoints		
[redacted]	[redacted]	[redacted]
Section 3.1 General Study Design and Study Schematic Diagram		
Once randomized, patients in the DS group will ~~have their rescue treatment switched to the~~be trained on the use of the Albuterol eMDPI DS~~,~~ (including instructions on how to use both the eMDPI and the App) and,	Once randomized, patients in the DS group will be trained on the use of the Albuterol eMDPI DS (including instructions on how to use both the eMDPI and the App)	Clarified the training that patients in the DS group receive on the Albuterol eMDPI and that additional

Original text with changes shown	New wording	Reason/Justification for change
upon demonstrating competency, will receive 2 Albuterol eMDPI devices for use as rescue bronchodilators to replace their rescue treatment during the study. Additional Albuterol eMDPI devices may be supplied during the treatment period, based on patients' needs.	and, upon demonstrating competency, will receive 2 Albuterol eMDPI devices for use as rescue bronchodilators to replace their rescue treatment during the study. Additional Albuterol eMDPI devices may be supplied during the treatment period, based on patients' needs.	devices may be supplied as necessary.
The CC group will be followed according to the clinical judgment of the investigator; the asthma of patients in the CC group will be managed in a manner consistent with the clinical judgement of the investigator and based on asthma management guidelines (eg, GINA). Similar to the management of the CC group, the DS group patients willThe DS group patients will then be followed by the investigational centers with the addition of objective information on Albuterol eMDPI usage being available to both patients and investigational centers through the App and the dashboard, respectively. The iHCPs will check the dashboard at least once a week and use this information, as per their clinical judgment, to make specific adjustments modify patients', in a manner consistent with their clinical judgement, based on asthma management. guidelines (eg, GINA). Clinically Driven Assessments for both groups, if necessary, should be arranged per the clinical judgement of the iHCP managing the patient and can be via a telephone call or an on-site visit.	The CC group will be followed according to the clinical judgment of the investigator; the asthma of patients in the CC group will be managed in a manner consistent with the clinical judgement of the investigator and based on asthma management guidelines (eg, GINA). Similar to the management of the CC group, the DS group patients will be followed by the investigational centers with the addition of objective information on Albuterol eMDPI usage being available to both patients and investigational centers through the App and the dashboard, respectively. The iHCPs will check the dashboard at least once a week and use this information, as per their clinical judgment, to modify patients' asthma management. Clinically Driven Assessments for both groups, if necessary, should be arranged per the clinical judgement of the iHCP managing the patient and can be via a telephone call or an on-site visit.	Clarified the management of the CC group.
At the end of the treatment period (12 weeks), final assessments of the DS and CC group patients will be made, as specified in Table 3. and ACT score registered for all patients. Patients, 18 years of age or older, will also complete the BMQ and BIPQ. Both DS patients, 18 years of age or older, and the investigational center personnel will complete the SUS questionnaire. DS patients will then return to their usual rescue inhalers, which they were on prior to study participation. A follow-up telephone call will be made by the investigational center to	At the end of the treatment period (12 weeks), final assessments of the DS and CC group patients will be made, as specified in Table 3. A follow-up telephone call will be made by the investigational center to all patients, 2 weeks later, and will confirm the DS group patients have returned to previous asthma treatments.	Revised to streamline presentation.

Original text with changes shown	New wording	Reason/Justification for change
all patients, 2 weeks later, and will confirm the DS group patients have returned to previous asthma treatments.		
Figure 2: Overall Study Schematic Diagram		
See New wording column.	The figure has been modified to reflect additional procedures for Clinically Driven Assessments.	Updated for consistency with new procedures in Table 3.
Section 3.2 Planned Number of Patients and Countries		
The study is expected to start in ~~Q2 2019~~ Q4 2020 and last until approximately ~~Q2 2020~~ Q4 2021.	The study is expected to start in Q4 2020 and last until approximately Q4 2021.	Updated the anticipated start and end dates of the study.
Section 3.5 Schedule of Study Procedures and Assessments		
Table 3 Study Procedures and Assessments		
See New wording column.	Table 3 Study Procedures and Assessments has been modified as described below: • The row for "Dispense test IMP to DS group" has been modified to include "Train." • A row has been added for the procedure "Remove App from the patient's smart device," to be done at the End of Treatment/Early Termination visit. • Xs have been added to indicate that assessment of adverse events/adverse device effects and concomitant medications will be performed during Clinically Driven Assessments and Unscheduled IMP Dispensing visits, if any. • An X has been added to indicate that test IMP collection and accountability will be performed during Unscheduled IMP Dispensing visits, if any.	Added to clarify and reflect additional procedures at the End of Treatment/Early Termination visit, Clinically Driven Assessments, and nd Unscheduled IMP Dispensing visits.

Original text with changes shown	New wording	Reason/Justification for change
[d] Patients will be provided the Test IMP, along with training on use and proper technique, by the investigational centers.	[d] Patients will be provided the Test IMP, along with training on use and proper technique, by the investigational centers.	Clarified the training that patients in the DS group receive on the Albuterol eMDPI.
[g] …. If a patient in the DS group ends the study prematurely, in addition to following up on ongoing AEs and concomitant medications, the investigational centersite will also confirm that the patient has returned to their previous asthma treatment.	[g] …. If a patient in the DS group ends the study prematurely, in addition to following up on ongoing AEs and concomitant medications, the investigational center will also confirm that the patient has returned to their previous asthma treatment.	Updated terminology for consistency across the protocol.
Section 5.1 Investigational Medicinal Products Used in the Study		
Patients At Visit 1, patients in the DS group will be trained on the use of the Albuterol eMDPI DS (including instructions on how to use both the eMDPI and the App) and, upon demonstrating competency, will receive 2 Albuterol eMDPI devices at visit 1. Patients will receive instructions for using the Albuterol eMDPI from the investigational center personnel use as rescue bronchodilators to replace their rescue treatment during the study. Additional Albuterol eMDPI devices may be supplied during the treatment period, based on patients' needs.	At Visit 1, patients in the DS group will be trained on the use of the Albuterol eMDPI DS (including instructions on how to use both the eMDPI and the App) and, upon demonstrating competency, will receive 2 Albuterol eMDPI devices for use as rescue bronchodilators to replace their rescue treatment during the study. Additional Albuterol eMDPI devices may be supplied during the treatment period, based on patients' needs.	Clarified the training that patients in the DS group receive on the Albuterol eMDPI and added that additional devices may be supplied as necessary.
Section 5.1.1 Test Investigational Medicinal Product		
Albuterol eMDPI (marketed in the US as PROAIR DIGIHALERRESPICLICK) is an inhalation-driven eMDPI containing a blend of albuterol sulfate and alpha-lactose monohydrate. Albuterol eMDPI is the result of adding an eModule electronic sensor to the Albuterol MDPI.	Albuterol eMDPI (marketed in the US as PROAIR DIGIHALER) is an inhalation-driven eMDPI containing a blend of albuterol sulfate and alpha-lactose monohydrate….	Updated to focus on DIGIHALER rather than RESPICLICK, as FDA-approved labeling for DIGIHALER is now available.
By consenting to enroll in the study, the patient must also download the smart device App (with the assistance of investigational center personnel), accept the smart device App's Privacy Notice and Terms of Use, and also agree to share his/her data to a provider-facing dashboard utilized by the iHCP and investigational center study team.	By consenting to enroll in the study, the patient must also download the smart device App (with the assistance of investigational center personnel), accept the smart device App's Privacy Notice and Terms of Use, and also agree to share his/her data to a provider-facing dashboard utilized by the iHCP and investigational center study team.	Clarified that investigational center personnel will provide assistance to download the App.

Original text with changes shown	New wording	Reason/Justification for change
At the end of treatment/ET visit (Visit 2), investigational center personnel will remove the App from the patient's smart device.	At the end of treatment/ET visit (Visit 2), investigational center personnel will remove the App from the patient's smart device.	Added sentence to reflect additional procedure at the End of Treatment/Early Termination visit.
Section 5.1 Investigational Medicinal Products Used in the Study		
Table 4: Investigational Medicinal Products Used in the Study		
See New wording column.	Table 4 Investigational Medicinal Products Used in the Study has been revised as described below: ● Unit dose strength has been revised to: "117 mcg of albuterol sulfate (equivalent to 97 mcg of albuterol base) from the device reservoir to provide a delivered dose of 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base)." ● Teva Pharmaceuticals Ireland was added to the Manufacturer row.	Clarified dose (nominal versus metered) and updated manufacturer.
Section 5.1.2 Medical Devices		
Instructions for medical device use are provided in the Study ~~Reference~~Pharmacy Manual.	Instructions for medical device use are provided in the Study Pharmacy Manual.	Updated reference to the source of information.
Section 5.1.2.1 Application		
The App gets environment information ~~from 1 or more web services~~ for the specific location of the patient.	The App gets environment information for the specific location of the patient.	Clarified meaning of environment information.
Section 5.2.3 Accountability		
Each IMP shipment will include a packing slip listing the contents of the shipment~~, return instructions,~~ and any applicable forms. …. Further guidance and information are provided in the Study ~~Reference~~Pharmacy Manual.	Each IMP shipment will include a packing slip listing the contents of the shipment and any applicable forms. …. Further guidance and information are provided in the Study Pharmacy Manual.	Updated reference to the source of information.
Section 5.3.1 Justification for Dose of Test Investigational Medicinal Product		
The prescribed dose of Albuterol eMDPI (now US FDA approved as PROAIR DIGIHALER) used in this study (ie, 90 mcg, 1 to 2 inhalations every 4 to 6 hours, as needed) was selected based on the prescribing information for PROAIR DIGIHALER~~,RESPICLICK, which has the~~	The prescribed dose of Albuterol eMDPI (now US FDA approved as PROAIR DIGIHALER) used in this study (ie, 90 mcg, 1 to 2 inhalations every 4 to 6 hours, as needed) was selected based on the	Updated to focus on DIGIHALER rather than RESPICLICK, as FDA-approved labeling for DIGIHALER is now available.

Original text with changes shown	New wording	Reason/Justification for change
~~same drug delivery design as Albuterol eMDPI.~~ PROAIR DIGIHALER~~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 EIB. For the relief of acute asthma symptoms, PROAIR DIGIHALER~~RESPICLICK~~ is recommended at a dosage of 2 inhalations (ie, 180 mcg of albuterol base ex-mouthpiece) repeated every 4 to 6 hours, as needed…. The recommended dosage for PROAIR DIGIHALER~~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 DIGIHALER~~RESPICLICK~~ is effective for the treatment or prevention of bronchospasm in adult and adolescent patients with obstructive airway disease.	prescribing information for PROAIR DIGIHALER. PROAIR DIGIHALER 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 EIB. For the relief of acute asthma symptoms, PROAIR DIGIHALER is recommended at a dosage of 2 inhalations (ie, 180 mcg of albuterol base ex-mouthpiece) repeated every 4 to 6 hours, as needed…. The recommended dosage for PROAIR DIGIHALER 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 DIGIHALER is effective for the treatment or prevention of bronchospasm in adult and adolescent patients with obstructive airway disease.	
Section 6.1.1 Asthma Control Test		
Detailed instructions for administering, scoring, and analyzing the ACT are provided in the ~~Study Reference Manual~~statistical analysis plan.	Detailed instructions for administering, scoring, and analyzing the ACT are provided in the statistical analysis plan.	Changed cross-reference, as there will not be a Study Reference Manual.
Section 7 Assessment of Safety		
In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, ~~device safety (as assessed by~~ adverse device effects, vital signs measurements, ~~and serious adverse device effects),~~ and use of concomitant medications. Adverse events are categorized by ICH guidelines, and adverse device effects are categorized and classified according to International Organization for Standardization (ISO) standard 14155:2011(E)~~, as shown in Table 5. Device deficiencies that are not associated with an adverse event are covered in Section 9 and Appendix F.(~~.	In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, adverse device effects, vital signs measurements, and use of concomitant medications. Adverse events are categorized by ICH guidelines, and adverse device effects are categorized and classified according to International Organization for Standardization (ISO) standard 14155:2011(E). Device deficiencies that are not associated with an adverse event	Text was updated to be consistent with the latest Teva protocol template.

Original text with changes shown	New wording	Reason/Justification for change
[Table 5 deleted] Device deficiencies that are not associated with an adverse event as well as those that have the potential to cause a serious adverse event are covered in Appendix F.	as well as those that have the potential to cause a serious adverse event are covered in Appendix F.	
Section 7.1.1 Definition of an Adverse Event		
• drug/drug, drug/device, or device/device interactions	• drug/drug, drug/device, or device/device interactions	Text was updated to be consistent with the latest Teva protocol template.
Section 7.1.5.2 Expectedness		
~~The sponsor will be responsible for determining whether an adverse event is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the reference safety information (RSI) in the IB described in Section 7.1. 6for the medical device used in this study.~~	[Text was deleted.]	Text was updated to be consistent with the latest Teva protocol template.
Section 7.1.5.3.1. Investigator Responsibility		
For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences form/MedWatch form/Extensible Markup Language file to the LSO/CRO for submission to the competent authorities, Independent Ethics Committee/Institutional Review Board (IEC/IRB), and investigators, according to regulations.	For all countries, the sponsor's GPSP will distribute the Council for International Organizations of Medical Sciences form/MedWatch form/Extensible Markup Language file to the LSO/CRO for submission to the competent authorities, Independent Ethics Committee/Institutional Review Board (IEC/IRB), and investigators, according to regulations.	Text was updated to be consistent with the latest Teva protocol template.
Section 7.1.6 Protocol-Defined Adverse Events of Special Interest		
Section 7.1.6 Protocol-Defined Adverse Events ~~Not for Expedited Reporting~~ of Special Interest ~~All adverse events will be reported according to regulatory requirements.~~	**Section 7.1.6 Protocol-Defined Adverse Events of Special Interest** [Sentence was deleted.]	Heading and text were updated to be consistent with the latest Teva protocol template.
Section 7.2 Adverse Device Effects		
An adverse device effect is an adverse event related to the use of an investigational medical device or a combination product.	An adverse device effect is an adverse event related to the use of an investigational medical device or a combination product.	Text was updated to be consistent with the latest Teva protocol template.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.2.1 Adverse Device Effect Reporting		
Adverse device effects (Figure 4) ~~and device deficiencies shall be reported in a study-specific adverse device effect form.~~ must be recorded on both ~~on~~ the source documentation and the CRF. ….The investigator and sponsor will record all relevant information regarding every adverse device effect/serious adverse device effect and device deficiency and will categorize each as guided in Section 7.2. . ~~Adverse device effects and device deficiencies will be listed in the clinical study report (CSR). Examples of adverse device effects and recommended actions to be taken are presented in Appendix F.~~ [Figure 4 moved to Section 7.2.2.1] The investigator should make an initial determination whether the adverse event may be related to a device deficiency. Adverse device effects and device deficiencies will be listed in the clinical study report (CSR).	Adverse device effects (Figure 4) must be recorded on both the source documentation and the CRF. ….The investigator and sponsor will record all relevant information regarding every adverse device effect/serious adverse device effect and device deficiency and will categorize each as guided in Section 7.2. The investigator should make an initial determination whether the adverse event may be related to a device deficiency. Adverse device effects and device deficiencies will be listed in the clinical study report (CSR).	Text was updated to be consistent with the latest Teva protocol template.
Section 7.2.2. Serious Adverse Device Effects		
A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (Section 7.1.5.1(~~or that might have led to any of these consequences if suitable action had not been taken, intervention had not been made, or if circumstances had been less opportune~~). An unanticipated serious adverse device effect is a serious adverse device effect that, by its nature, incidence, severity, or outcome, has not been listed in ~~Section 7.1. 6of this protocol.~~Appendix F (Appendix Table ~~7~~1 and Appendix Table ~~8~~2).	A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (Section 7.1.5.1). An unanticipated serious adverse device effect is a serious adverse device effect that, by its nature, incidence, severity, or outcome, has not been listed in Appendix F (Appendix Table 1 and Appendix Table 2).	Text was updated to be consistent with the latest Teva protocol template.
Section 7.2.2.1. Serious Adverse Device Effect Reporting		
The investigator will report to the sponsor, without unjustified delay, all serious adverse device effects (within 24 hours) ~~and device deficiencies that could have led to a serious adverse device effect;~~); this information shall be promptly followed by detailed written reports as described below.	The investigator will report to the sponsor, without unjustified delay, all serious adverse device effects (within 24 hours); this information shall be promptly followed by detailed written reports as described below.	Text was updated to be consistent with the latest Teva protocol template.

Original text with changes shown	New wording	Reason/Justification for change
The process and contact details for serious adverse device effect reporting are the same as for serious adverse event reporting provided in Section 7.1.5.3. Events shall be reported to the ~~Ethics Committee~~IEC/IRB by the investigator and to the regulatory authorities by the sponsor using the appropriate form according to ~~the timelines detailed below~~national and local regulations. The ~~following events are considered reportable events (Figure 4~~investigator should use Appendix F (Appendix Table ~~7~~1 and Appendix Table ~~8~~2)~~:~~ ~~•~~ any ~~Table 8)~~ to make an initial determination whether the serious adverse event ~~or serious adverse device effect~~ ~~•~~ any may be related to a device deficiency ~~that might have led to a serious adverse device effect if~~. [Figure 4 Decision Tree for Adverse Events and Adverse Device Effects Classification; moved from Section 7.2.1] ~~•~~ suitable action had not been taken (or) ~~•~~ intervention had not been made (or) ~~•~~ if circumstances had been less fortunate ~~•~~ new findings/updates in relation to already reported events. ~~The timelines for reporting are as follows:~~ ~~•~~ for a serious adverse event or serious adverse device effect that indicates an imminent risk of death, serious injury, or serious illness and requires prompt remedial action for patients, users, or other persons ~~•~~ immediately, but not later than 2 calendar days after awareness by the sponsor of a new reportable event or of new information in relation with an already reported event. ~~•~~ for any other reportable events as described above or a new finding/update ~~•~~ immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event. ~~All serious adverse device effects will be listed in the CSR.~~	The process and contact details for serious adverse device effect reporting are the same as for serious adverse event reporting provided in Section 7.1.5.3. Events shall be reported to the IEC/IRB by the investigator and to the regulatory authorities by the sponsor using the appropriate form according to national and local regulations. The investigator should use Appendix F (Appendix Table 1 and Appendix Table 2) to make an initial determination whether the serious adverse event may be related to a device deficiency. [Figure 4 Decision Tree for Adverse Events and Adverse Device Effects Classification; moved from Section 7.2.1]	

Original text with changes shown	New wording	Reason/Justification for change
Section 7.4. Medication Error and Special Situations Related to the Investigational Medicinal Product		
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~~ patient's, ~~or as a deviation, in the patients~~[2] source documents (Appendix C), regardless of whether or not an adverse event occurs as a result. … ~~5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.~~	Any administration of IMP that is not in accordance with the study protocol should be reported in the patient's source documents (Appendix C), regardless of whether or not an adverse event occurs as a result. … [Deleted item 5]	Text was updated to be consistent with the latest Teva protocol template.
Section 9 Assessment of Device Performance		
[Deleted section]	[Deleted section]	Text was updated to be consistent with the latest Teva protocol template by moving the content of this section to Appendix F Product Complaints.
Section 9.2.1 Intent-to-Treat Analysis Set		
The intent-to-treat (ITT) ~~This~~ analysis set will include all randomized patients. ~~who were enrolled in the study (signed ICF) and meet inclusion/exclusion criteria. A patient is considered enrolled according to the status reported in the database.~~	The intent-to-treat (ITT) analysis set will include all randomized patients.	Clarified this analysis set.
Section 9.2.2 Modified Intent-to-Treat Analysis Set		
The modified intent-to-treat (mITT)~~This~~ analysis set is a subset of the ITT analysis set including~~and will~~ only ~~include all enrolled~~ patients who receive~~completed~~ at least 1 dose of IMP (IMP is albuterol eMDPI for the DS group and standard-of-care albuterol-administering rescue medication for the CC group) and at least 1 postbaseline assessment on any of~~as recorded per the CRF and confirmed by the status reported in~~ the study endpoints (primary, secondary, or exploratory). ~~database. Data collected from patients after treatment discontinuation will not be included in the modified intent-to-treat (mITT) analysis set.~~	The modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP (IMP is albuterol eMDPI for the DS group and standard-of-care albuterol-administering rescue medication for the CC group) and at least 1 postbaseline assessment on any of the study endpoints (primary, secondary, or exploratory).	Clarified this analysis set.
Section 9.2.3 Safety Analysis Set		

Original text with changes shown	New wording	Reason/Justification for change
This analysis set will include all ~~randomized~~ patients in the DS group who receive at least 1 dose of IMP and all patients in the CC group.	This analysis set will include all patients in the DS group who receive at least 1 dose of IMP and all patients in the CC group.	Clarified this analysis set.
Section 9.4.1 Patient Disposition		
Data from patients screened; patients screened but not randomized~~enrolled~~ and reason for not being randomized~~non-enrollment~~; patients in the ITT analysis set~~who are enrolled~~; patients in the ITT analysis set~~enrolled but~~ who did not attempt to download the App; patients in the ITT analysis set~~enrolled but~~ who did not use the inhaler; patients in the ~~ITT,~~ mITT and safety analysis sets; patients who completed the study; and patients who withdrew from the study and the reason for withdrawal will be summarized using descriptive summary statistics (number, %).	Data from patients screened; patients screened but not randomized and reason for not being randomized; patients in the ITT analysis set; patients in the ITT analysis set who did not attempt to download the App; patients in the ITT analysis set who did not use the inhaler; patients in the mITT and safety analysis sets; patients who completed the study; and patients who withdrew from the study and the reason for withdrawal will be summarized using descriptive summary statistics (number, %).	Clarified how patient disposition will be summarized.
Section 9.5.4.1 Primary Analysis		
3. Summary measure: A successful differentiation between the 2 groups will be determined by a Bayesian posterior probability for $\beta_1 \geq 0$ greater than 0.95 (1-sided). The following statistical methods will be utilized:	3. Summary measure: A successful differentiation between the 2 groups will be determined by a Bayesian posterior probability for $\beta_1 > 0$ greater than 0.95 (1-sided). The following statistical methods will be utilized:	Clarified β_1.
Section 9.5.2 Secondary Endpoints		
o addition of ~~an oral or parenteral~~ a systemic corticosteroid medication for asthma or another controller, including a LAMA or biologics	o addition of a systemic corticosteroid medication for asthma or another controller, including a LAMA or biologics	Revised for clarity and specificity.
Section 9.5.3 Exploratory/Other Endpoints		
[redacted]	[redacted]	[redacted]
Section 10 Quality Control and Quality Assurance		
Refer to Appendix F for the definition of a clinical product complaint or device deficiency and investigator responsibilities	Refer to Appendix F for the definition of a clinical product complaint or device deficiency and investigator responsibilities in	Text was updated to be consistent with the latest Teva protocol template.

Original text with changes shown	New wording	Reason/Justification for change
in the management of a clinical product complaint or device deficiency.	the management of a clinical product complaint or device deficiency.	
Appendix A Clinical Laboratories and Other Departments and Institutions		
[redacted]	[redacted]	[redacted]
Appendix B Study Procedures and Assessments by Visit		
1. Procedures for Screening/Baseline Visit (Visit 1, Day 1) See New wording column.	1. Procedures for Screening/Baseline Visit (Visit 1, Day 1) • train patients in the DS group on use and proper technique of the albuterol multidose dry powder inhaler with integrated electronic module (Albuterol eMDPI)	Clarified the training that patients in the DS group receive on the Albuterol eMDPI.
3. Procedures for End of Treatment/Early Termination Visit (Visit 2, Day 84 + up to 7 days) • remove the App from the patient's smart device	3. Procedures for End of Treatment/Early Termination Visit (Visit 2, Day 84 + up to 7 days) • remove the App from the patient's smart device	Added an additional procedure to the End of Treatment/Early Termination visit.
4. Procedures for Clinically Driven Assessment(s) (If Necessary) See New wording column.	4. Procedures for Clinically Driven Assessment(s) (If Necessary) • conduct adverse events and adverse device effects inquiry • conduct concomitant medication inquiry	Added additional procedures to these optional visits.
5. Procedures for an Unscheduled Investigational Medicinal Product Dispensing Visit See New wording column.	5. Procedures for an Unscheduled Investigational Medicinal Product Dispensing Visit • conduct adverse events and adverse device effects inquiry • conduct concomitant medication inquiry • perform Albuterol eMDPI collection and accountability	Added additional procedures to these optional visits.
APPENDIX F. PRODUCT COMPLAINTS		
I. Clinical Product Complaints / Device Deficiency …. Each investigational center will be responsible for reporting a possible clinical	I. Clinical Product Complaints / Device Deficiency …. Each investigational center will be responsible for reporting a	Text was updated to be consistent with the latest Teva protocol template.

Original text with changes shown	New wording	Reason/Justification for change
product complaint by completing the product complaint form ~~(adverse device effect form)~~ provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue. For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (or item) be sent back to the sponsor for investigative testing whenever possible. …. The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (Section II), and any actions taken to resolve the complaint and to preserve the safety of the patient. …. See New wording column.	possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue. For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (or item) be sent back to the sponsor for investigative testing whenever possible. …. The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (Section II), and any actions taken to resolve the complaint and to preserve the safety of the patient. …. II. Assessment of Device Performance Device performance will be assessed by device deficiencies and product complaints. A device deficiency is defined as any inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety, or performance (Appendix Figure 1). This definition includes malfunctions, use errors, inadequate labeling (eg, unintelligible label, incorrect expiry date), and product complaints that are related to the eMDPI. The investigator should use Appendix Table 1 and Appendix Table 2 to help make an initial determination whether the device deficiency could have led to a serious adverse event and notify	

Original text with changes shown	New wording	Reason/Justification for change
	the sponsor by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com. Device deficiencies with potential serious adverse device effect are defined as deficiencies that might have led to a serious adverse device effect if (Appendix Figure 1): • suitable action had not been taken (or) • intervention had not been made (or) • circumstances had been less fortunate [Inserted Appendix Figure 1: Decision Tree for Device Deficiencies, Appendix Table 1: Potential Use-Related Deficiencies that Could Lead to Serious Adverse Events, and Appendix Table 2: Potential Design-Related Deficiencies that Could Lead to Serious Adverse Events]	

16.3. Amendment 02 Dated 26 February 2019

The primary reason for this amendment is to change unscheduled visits or telephone calls to Clinically Driven Assessments, if necessary, to clarify that these visits were generated by the interaction between HCP and the data provided by the dashboard. Other nonsignificant 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.

Table 3 (Study Procedures and Assessments), Table 4 (Investigational Medicinal Products Used in the Study), and Figure 2 (Overall Study Schematic Diagram) have been revised to reflect changes described below.

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Title page		
Lay person title: A Study to Test if Using the Albuterol eMDPI System is Effective in Getting Better Control of Asthma in Patients at Least 13 Years of Age ~~with Asthma~~ Compared to Usual Care	Lay person title: A Study to Test if Using the Albuterol eMDPI System is Effective in Getting Better Control of Asthma in Patients at Least 13 Years of Age Compared to Usual Care	Deleted text to minimize redundancy.
© 2019 ~~2018~~ Teva Branded Pharmaceutical Products R&D, Inc.	© 2019 Teva Branded Pharmaceutical Products R&D, Inc.	Revised with correct year.
List of Abbreviations (Other sections affected by this change: Sections 1.3.1, 3.1, and 3.5 and Appendix B)		
~~Brief Medication~~ Beliefs about Medicines Questionnaire	Beliefs about Medicines Questionnaire	Revised to correct the title of the questionnaire.
Section 1.1 Introduction (Other sections affected by this change: Sections 5.1.1 and 5.3.1)		
On 21 December 2018, the US FDA approved Albuterol eMDPI as PROAIR® DIGIHALER™ (albuterol sulfate inhalation powder), 90 mcg of albuterol base per actuation, for treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm in patients 4 years of age and older.	On 21 December 2018, the US FDA approved Albuterol eMDPI as PROAIR® DIGIHALER™ (albuterol sulfate inhalation powder), 90 mcg of albuterol base per actuation, for treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm in patients 4 years of age and older.	Added text due to FDA approval.
Teva has developed ~~is developing~~ the eModule as part of a Digital System (DS) to assist a patient with asthma to appropriately use the eMDPI inhaler.	Teva has developed the eModule as part of a Digital System (DS) to assist a patient with asthma to appropriately use the eMDPI inhaler.	Revised to make past tense.
Section 2.1 Primary and Secondary Study Objectives and Endpoints (Other sections affected by this change: Sections 10.5.1.)		
The primary endpoint is the proportion of patients for DS and CC group patients achieving meaningful improvement defined as: • the proportion of patients with an ACT score greater than or equal to 20 at the end of the 12-week treatment period OR • the proportion of patients with an increase of at least 3 ~~ACT~~ units on	The primary endpoint is the proportion of patients for the DS and CC groups achieving meaningful improvement, which is defined as an Asthma Control Test (ACT) score greater than or equal to 20 at the end of the 12 week treatment period or an increase of at least 3 units on the ACT score from baseline at the end of the 12-week treatment period.	Revised to change format from bulleted list to paragraph, and ACT text revised for clarity.

Original text with changes shown	New wording	Reason/Justification for change
the ACT score from baseline at the end of the 12-week treatment period		
Section 2.1 Primary and Secondary Study Objectives and Endpoints (Other sections affected by this change: Section 10.5.2)		
o number of discussions between patient and HCP regarding inhaler technique or adherence	o number of discussions between patient and HCP regarding inhaler technique or adherence	Revised for clarity and specificity.
Section 2.1 Primary and Secondary Study Objectives and Endpoints (Other sections affected by this change: Section 10.5.2)		
o addition of an oral or ~~biologic~~ parenteral medication for asthma,~~)~~ including biologics	o addition of an oral or parenteral medication for asthma, including biologics	Revised for clarity and specificity.
Section 2.2. Exploratory Objectives and Endpoints (Other sections affected by this change: Section 10.5.3)		
[redacted]	[redacted]	[redacted]
Section 2.2. Exploratory Objectives and Endpoints (Other sections affected by this change: Section 10.5.3)		
[redacted]	[redacted]	[redacted]
Section 3.1. General Study Design and Study Schematic Diagram (Other sections affected by this change: Section 3.5 and Appendix B)		
~~Unscheduled visits or telephone calls~~ Clinically Driven Assessments, if necessary, should be arranged~~,~~ per the clinical judgement of the iHCP~~,~~ managing the patient and can be via a telephone call or an on-site visit.	Clinically Driven Assessments, if necessary, should be arranged per the clinical judgement of the iHCP managing the patient and can be via a telephone call or an on-site visit.	Revised for clarity.
Section 3.1 General Study Design and Study Schematic Diagram		
A follow-up telephone call will be made by the investigational center to all patients, 2 weeks later, ~~to~~ and will confirm the DS group patients have ~~patient has~~ returned to previous asthma treatments.	A follow-up telephone call will be made by the investigational center to all patients, 2 weeks later, and will confirm the DS group patients have returned to previous asthma treatments.	Revised for clarity.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.2 Planned Number of Patients and Countries		
The study is expected to start in Q2 ~~Q1~~ 2019 and last until approximately Q2 ~~Q1~~ 2020.	The study is expected to start in Q2 2020 and last until approximately Q2 2021.	Revised with correct quarter.
Section 3.5 Schedule of Study Procedures and Assessments (Other sections affected by this change: Section , 4.3, 5.1, 5.6, and Appendix B)		
End of ~~Study~~ Treatment	End of Treatment	Revised for accuracy since End of Study is defined as the follow-up telephone call for the last patient.
Table 3 Study Procedures and Assessments		
g The follow-up telephone call will be made to all patients, including those who end the study prematurely (except patients who withdraw consent). If a patient in the DS group ends the study prematurely, in addition to following up on ongoing AEs and concomitant medications, the site will also confirm that the patient has returned to their previous asthma treatment.	g The follow-up telephone call will be made to all patients, including those who end the study prematurely (except patients who withdraw consent). If a patient in the DS group ends the study prematurely, in addition to following up on ongoing AEs and concomitant medications, the site will also confirm that the patient has returned to their previous asthma treatment.	Added footnote g for clarity.
Section 4.2. Patient Exclusion Criteria		
d. The patient has a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) or Asthma-COPD Overlap (ACO).	d. The patient has a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) or Asthma-COPD Overlap (ACO).	Added an additional exclusion criterion.
Section 4.5 Rescreening		
If the patient is rescreened, the ~~an~~ informed consent form (ICF) will ~~may~~ need to be ~~resigned~~ re-signed.	If the patient is rescreened, the informed consent form (ICF) will need to be re-signed.	Revised for accuracy.
Section 5.1.2.3 Dashboard		
The data available on the dashboard are the inhaler use data ~~from the App~~ and patient self-assessments from the App.	The data available on the dashboard are the inhaler use data and patient self-assessments from the App.	Revised for accuracy.
Section 5.2.3. Accountability		
All ~~E~~empty, partially used, and unused inhalers will be collected at the end of the study~~, and all data will be downloaded from the inhalers.~~ and will be returned to the sponsor or designee per sponsor instructions.	All empty, partially used, and unused inhalers will be collected at the end of the study and will be returned to the sponsor or designee per sponsor instructions.	Edited text to provide clarity.

Original text with changes shown	New wording	Reason/Justification for change
Table 4 Investigational Medicinal Products Used in the Study		
Oral inhalation	Oral inhalation	Revised for accuracy and specificity to distinguish from nasal inhalation.
Section 6.1.1. Asthma Control Test		
The scores span the continuum of poor control of asthma (score of 5) to complete control of asthma (score of 25), with a cutoff score of 19 and below indicating patients with poorly controlled asthma (Schatz et al 2006).	The scores span the continuum of poor control of asthma (score of 5) to complete control of asthma (score of 25), with a cutoff score of 19 and below indicating patients with poorly controlled asthma (Schatz et al 2006).	Revised for accuracy.
Section 6.1.2. Beliefs about Medicines Questionnaire		
6.1.2. ~~Brief Medication~~ Beliefs about Medicines Questionnaire ~~The BMQ is a self reporting tool to measure screening adherence and barriers to adherence. The tool includes a 5-item Regimen Screen that asks patients how they took each medication in the past week, a 2-item Belief Screen that asks about drug effects and bothersome features, and a 2-item Recall Screen about potential difficulties remembering. The BMQ will be answered by patients,~~ The BMQ is used to assess cognitive representations of medicine (Horne, Weinman, and Hankins 1999). The BMQ-Specific (BMQ-S11) is an 11-item questionnaire that assesses representation of medication prescribed for personal use and the BMQ-General assesses beliefs about medicines in general. For the purposes of this study, the BMQ-S11 will be completed by patients, 18 years of age or older, at the investigational center at Visit 1, Visit 2, or at the ET visit.	**6.1.2. Beliefs about Medicines Questionnaire** The BMQ is used to assess cognitive representations of medicine (Horne, Weinman, and Hankins 1999). The BMQ-Specific (BMQ-S11) is an 11-item questionnaire that assesses representation of medication prescribed for personal use and the BMQ-General assesses beliefs about medicines in general. For the purposes of this study, the BMQ-S11 will be completed by patients, 18 years of age or older, at the investigational center at Visit 1, Visit 2, or at the ET visit.	Revised to correct the name and description of the questionnaire and to add reference.
Section 7.1.1. Definition of an Adverse Event		
A CAE will be defined by 1 of the following: 1) in-patient hospitalization because of asthma, 2) emergency treatment because of asthma, 3) a worsening of asthma symptoms leading to the use of prednisone or systemic corticosteroids for 3 days or more, or 4) a reduction in FEV1 of 20% or greater.	A CAE will be defined by 1 of the following: 1) in-patient hospitalization because of asthma, 2) emergency treatment because of asthma, 3) a worsening of asthma symptoms leading to the use of prednisone or systemic corticosteroids for 3 days or more, or 4) a reduction in FEV1 of 20% or greater.	Added text for clarity and specificity.

Original text with changes shown	New wording	Reason/Justification for change
Section 7.1.6. Protocol-Defined Adverse Events Not for Expedited Reporting		
All adverse events will be reported according to regulatory requirements. No protocol-defined adverse events of special interest were identified for this study.	All adverse events will be reported according to regulatory requirements. No protocol-defined adverse events of special interest were identified for this study.	Added for clarity.
Section 7.3. Pregnancy		
All pregnancies of women participating in the study ~~and female partners of men participating in the study~~, that occur during the study, or within at least 5 half-lives or 30 days for unknown 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.	All pregnancies of women participating in the study, that occur during the study, or within at least 5 half-lives or 30 days for unknown 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.	Deleted text to minimize redundancy.
Section 10.1. Sample Size and Power Considerations (Other sections affected by this change: Section 16)		
With this sample size and assuming a true absolute difference in proportions (treatment effect as the estimated response rate for the CC group is 60% and for the DS group is 73%) between the groups of at least 13%, the probability that the posterior probability will be at least 95% is 0.77 (power) (analogous to 1-sided p-value < 0.05) (Merchant et al 2016).	With this sample size and assuming a true absolute difference in proportions (treatment effect as the estimated response rate for the CC group is 60% and for the DS group is 73%) between the groups of at least 13%, the probability that the posterior probability will be at least 95% is 0.77 (power) (analogous to 1-sided p-value < 0.05) (Merchant et al 2016).	Added for clarity and specificity.
Section 10.5. Analyses		
~~Efficacy~~ analysis	analysis	Deleted text since efficacy of the drug product will not be evaluated in this study.
Appendix A Clinical Laboratories and Other Departments and Institutions		

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	Added for completeness.
Appendix B Study Procedures and Assessments by Visit		
The following procedures and assessments will be performed at ~~unscheduled visits and unscheduled phone calls~~ a Clinically Driven Assessment: • ~~conduct adverse events and adverse device effects inquiry~~ • ~~conduct concomitant medication inquiry~~ • ~~record reason for unscheduled visit or call~~ • ~~measure vital signs (unscheduled visit only)~~ • dispense Albuterol eMDPI as needed (~~unscheduled visit only~~ if on-site and necessary) • ~~perform Albuterol eMDPI collection and accountability (unscheduled visit only)~~ • ~~review patient compliance~~ • iHCP asks Asthma Management questions	The following procedures and assessments will be performed at a Clinically Driven Assessment: • iHCP asks Asthma Management questions • dispense Albuterol eMDPI as needed (if on-site and necessary)	Revised to align with Table 3, and edited order of bullets to prioritize Asthma Management questions.
5. Procedures for an Unscheduled Investigational Medicinal Product Dispensing Visit The following procedures and assessments will be performed at an unscheduled IMP dispensing visit: • dispense test investigational medicinal product (IMP) to DS group patients	5. Procedures for an Unscheduled Investigational Medicinal Product Dispensing Visit The following procedures and assessments will be performed at an unscheduled IMP dispensing visit: • dispense test investigational medicinal product (IMP) to DS group patients	Added text to align with Table 3.
Appendix C Quality Control and Quality Assurance		
Protocol deviations ~~violations~~	Protocol deviations	Edited due to template change.

16.4. Amendment 01 Dated 13 December 2018

The primary reason for this amendment is the deletion of inclusion criterion “d”. This amendment is considered to be significant (ie, requires approval by CA, IEC, and/or IRB) by the sponsor’s Authorized Representative. Other nonsignificant 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.

Table 3 (Study Procedures and Assessments) and Figure 2 (Overall Study Schematic Diagram) have been revised to reflect changes described below.

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Title page (Other sections affected by this change: Investigator Agreement, Coordinating Investigator Agreement, Sections 3.1 and 4.1)		
CONNected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 1 ("CONNECT 1"), a 12-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study to Evaluate the Effectiveness of the Albuterol eMDPI Digital System, to Optimize Outcomes in Patients at Least ~~12~~13 Years of Age or Older with Asthma	**CONN**ected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 1 ("CONNECT 1"), a 12-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study to Evaluate the Effectiveness of the Albuterol eMDPI Digital System, to Optimize Outcomes in Patients at Least 13 Years of Age or Older with Asthma	Minimum age changed to match the minimum age requirement for use of the App.

Original text with changes shown	New wording	Reason/Justification for change
Title page		
This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, Inc and/or its affiliates.	This document contains confidential and proprietary information (including confidential commercial information pursuant to 21CFR§20.61) and is a confidential communication of Teva Branded Pharmaceutical Products R&D, Inc and/or its affiliates.	Added by Teva legal.
List of Abbreviations		
~~OCS oral corticosteroid~~	ET Early Termination MID minimally important difference RTSM Randomization and Trial Supply Management	Abbreviation OCS deleted – no longer in text Abbreviations ET, MID, and RTSM added
Section 1.1 Introduction (Other section affected by this change: Section 5.1.1)		
From the App, data may be transmitted to the Digital Health Platform (DHP), which consists of a cloud solution, and then to a ~~and~~ provider-facing dashboard.	From the App, data may be transmitted to the Digital Health Platform (DHP), which consists of a cloud solution, and then to a provider-facing dashboard.	Reworded to clarify that the dashboard is not part of the DHP.
Section 1.1 Introduction (Other sections affected by this change: Section 1.3.1, 2.1, 6.1.4, and 10.5.2)		
The study will also assess mean weekly SABA usage and the number of SABA-free days, the asthma management actions of investigational heath care providers (iHCPs) using the dashboard as part of the DS, and will collect information using patient questionnaires that focus on patients' beliefs and perceptions about their disease and inhaler satisfaction, as well as patient and investigati~~ve~~ional center personnel questionnaires on system usability.	The study will also assess mean weekly SABA usage and the number of SABA-free days, the asthma management actions of investigational heath care providers (iHCPs) using the dashboard as part of the DS, and will collect information using patient questionnaires that focus on patients' beliefs and perceptions about their disease and inhaler satisfaction, as well as patient and investigational center personnel system usability.	Corrected wording and added wording to clarify that the investigational center personnel will also complete a SUS regarding their interactions with the dashboard.

Original text with changes shown	New wording	Reason/Justification for change
Section 1.3.1 Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s) (Other sections affected by this change: Sections 2.1, 3.1, 6.1.1, 6.1.2, 6.1.3, 6.1.4, 10.5.2, and Appendix B)		
In addition to assessing the technical reliability experienced by patients using the Albuterol eMDPI DS, the study also uses 2 patient questionnaires, the Brief Medication Questionnaire (BMQ) and the Brief Illness Perception Questionnaire (BIPQ) for all patients, 18 years of age or older, in both groups, as well as the System Usability Scale (SUS) for patients, 18 years of age or older, in the DS group and investigational center personnel to complete.	In addition to assessing the technical reliability experienced by patients using the Albuterol eMDPI DS, the study also uses 2 patient questionnaires, the Brief Medication Questionnaire (BMQ) and the Brief Illness Perception Questionnaire (BIPQ) for all patients, 18 years of age or older, in both groups, as well as the System Usability Scale (SUS) for patients, 18 years of age or older, in the DS group and investigational center personnel to complete.	Age of 18 years or older added to descriptions of the BMQ, BIPQ, and SUS questionnaires since these questionnaires are not validated in patients under 18 years of age.

Original text with changes shown	New wording	Reason/Justification for change
Section 2.2 Exploratory Objectives and Endpoints (Other section affected by this change: Section 3.1)		
[redacted]	[redacted]	[redacted]
Section 3.1 General Study Design and Study Schematic Diagram (Other sections affected by this change: Section 5.8 and Appendix B)		
Patients with suboptimal asthma control will be enrolled in the study and randomized in a 1:1 ratio to 1 of 2 parallel groups stratified by investigational center: DS group patients utilizing the Albuterol eMDPI DS, including inhaler, App, DHP (Cloud solution), and dashboard, and CC group patients who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period. Similar data will be collected regarding outcomes for the CC group: ACT after 12 to 14 weeks, BMQ and BIPQ responses, and the frequency of CAEs ~~(moderate and/or severe).~~ …. A baseline ACT score for all patients, and BMQ~~,~~ and BIPQ responses for patients 18 years of age or older will be collected.	Patients with suboptimal asthma control will be enrolled in the study and randomized in a 1:1 ratio to 1 of 2 parallel groups stratified by investigational center: DS group patients utilizing the Albuterol eMDPI DS, including inhaler, App, DHP (Cloud solution), and dashboard, and CC group patients who will be treated with their standard of care albuterol-administering rescue inhalers and will not use the DS during the treatment period. Similar data will be collected regarding outcomes for the CC group: ACT after 12 to 14 weeks, BMQ and BIPQ responses, and the frequency of CAEs. …. A baseline ACT score for all patients, and BMQ and BIPQ responses for patients 18 years of age or older will be collected.	Stratifying by investigational center in the analysis model to adjust for investigational center difference if there is any. "for all patients" added to ACT score for clarity.
Section 3.1 General Study Design and Study Schematic Diagram (Other section affected by this change: Appendix B)		
Patients in the CC group will be reimbursed or given a voucher to use to purchase their existing rescue medications.	Patients in the CC group will be reimbursed or given a voucher to use to purchase their existing rescue medications.	Added the option of reimbursement.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.1 General Study Design and Study Schematic Diagram		
For all patients, at Visit 2 and at each unscheduled visit or telephone call, the iHCP will record answers to ~~various~~ Asthma Management questions regarding what interventions occurred as a consequence of the telephone call or visit, including discussions regarding adherence, or inhaler technique, treatment adjustments, or additions of new treatments, including biologic medication usage.	For all patients, at Visit 2 and at each unscheduled visit or telephone call, the iHCP will record answers to Asthma Management questions regarding what interventions occurred as a consequence of the telephone call or visit, including discussions regarding adherence, or inhaler technique, treatment adjustments, or additions of new treatments, including biologic medication usage.	Assigned a name to the iHCP questions.
Section 3.2 Planned Number of Patients and Countries		
Planned Study Period: The study is expected to start in Q1/2019 and last until approximately Q1/2020.	**Planned Study Period:** The study is expected to start in Q1 2019 and last until approximately Q1 2020.	Virgule removed and dates corrected under Study Duration.
Section 4 Selection and Withdrawal of Patients		
	Changes to inclusion or exclusion criteria are indicated below and detailed in Section 17.	Sentence added per amendment template.
Section 4.1 Patient Inclusion Criteria		
c. The patient is currently on treatment with an ~~moderate- to high-dose~~ ICS with a long-acting beta$_2$ agonist (LABA).	c. The patient is currently on treatment with an ICS with a long-acting beta$_2$ agonist (LABA).	Deleted "moderate to high dose". Any amount of ICS with LABA is acceptable.
~~d. The patient has been receiving the current asthma treatment in the investigational center for less than or equal to 12 weeks prior to informed consent.~~		Deleted "d" to not restrict the target population who will use the DS and changed the letters of the remaining inclusion criteria to update them accordingly.
f. The patient can read and communicate in English and is familiar with and is willing to use his/her own smart device and download and use the App.	f. The patient can read and communicate in English and is familiar with and is willing to use his/her own smart device and download and use the App.	Revised "f" since the App is only available in English.

Original text with changes shown	New wording	Reason/Justification for change
Section 4.2 Patient Exclusion Criteria		
f. The patient is currently being treated with ~~oral corticosteroids (OCS)~~ systemic corticosteroids (oral, intramuscular, or intravenous) or has been treated within the last 30 days.	f. The patient is currently being treated with systemic corticosteroids (oral, intramuscular, or intravenous) or has been treated within the last 30 days.	Exclusion criterion expanded to include other types of corticosteroids.
Section 4.3 Withdrawal Criteria and Procedures for the Patient		
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/or adverse device effect page and the termination page of the CRF will be completed at that time.	The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; the adverse events page and/or adverse device effect page and the termination page of the CRF will be completed at that time.	Sentence corrected to include the adverse device effect page as a CRF page to be completed at withdrawal.
Section 4.5 Rescreening		
A patient who is screened but not enrolled within 7 days of screening, because ~~inclusion and exclusion criteria were not met~~ he/she did not satisfy inclusion/exclusion criteria or enrollment did not occur within the specified time, may be considered for rescreening once if, for example, there is a change in the patient's medical background or a modification of study inclusion and exclusion criteria.	A patient who is screened but not enrolled within 7 days of screening, because he/she did not satisfy inclusion/exclusion criteria or enrollment did not occur within the specified time, may be considered for rescreening once if, for example, there is a change in the patient's medical background or a modification of study inclusion and exclusion criteria.	Revised because the patient could not meet both inclusion and exclusion criteria. Reworded for clarity.
Section 5.1.1 Test Investigational Medicinal Product		
The information from the eModule may be transmitted wirelessly (Bluetooth Low Energy) to an App. From the App, data may be transmitted to the DHP, which consists of a cloud solution, and then to a dashboard. This allows the patient and/or the caregiver to track when and how well the inhaler was used. By consenting to enroll in the study, the patient must also download the smart device App (with the assistance of investigational site personnel), accept the smart device	The information from the eModule may be transmitted wirelessly (Bluetooth Low Energy) to an App. From the App, data may be transmitted to the DHP, which consists of a cloud solution, and then to a dashboard. This allows the patient and/or the caregiver to track when and how well the inhaler was used. By consenting to enroll in the study, the patient must also download the smart device App (with the assistance of	Paragraph moved from earlier in this section to create better flow into new paragraph. Teva Legal and Data Privacy provided more precise language surrounding privacy and terms of use.

Original text with changes shown	New wording	Reason/Justification for change
App's Privacy Notice and Terms of Use, and also agree to share his/her data to a provider-facing dashboard utilized by the iHCP and investigational center study team. An ICF will be provided to the patients which will elaborate, among other ways, Teva's ways of use and storing of patient data collected through the smart device App. The patient will be entering into a direct contractual relationship with Teva which will govern, among other things, Teva's rights to use and store patient data collected through the smart device App. If the patient does not accept the smart device App's Privacy Notice and Terms of Use and does not also agree to share their data to the provider-facing dashboard utilized by the iHCP and investigational center study team, then the patient cannot enroll in the study.	investigational site personnel), accept the smart device App's Privacy Notice and Terms of Use, and also agree to share his/her data to a provider-facing dashboard utilized by the iHCP and investigational center study team. An ICF will be provided to the patients which will elaborate, among other ways, Teva's ways of use and storing of patient data collected through the smart device App. The patient will be entering into a direct contractual relationship with Teva which will govern, among other things, Teva's rights to use and store patient data collected through the smart device App. If the patient does not accept the smart device App's Privacy Notice and Terms of Use and does not also agree to share their data to the provider-facing dashboard utilized by the iHCP and investigational center study team, then the patient cannot enroll in the study.	
Section 5.1.2.1 Application		
The intention of the smart device App is to engage patients with ~~respiratory disease~~ asthma and/or COPD (and their caregivers) by tracking medication usage, raising awareness of medication use patterns, allowing users to self-assess their respiratory symptoms on a daily basis, sharing information on local environmental conditions, and producing user reports to review their data over time. The software consists of a ~~mobile~~ smart device application compatible for iPhone operating systems (iOS) and Android operating systems that will store data locally on the patient's smart device. The App will receive a patient's health data automatically from the inhaler devices via Bluetooth on a smart device. The smart device camera will be used for scanning and pairing. This data	The intention of the smart device App is to engage patients with asthma and/or COPD (and their caregivers) by tracking medication usage, raising awareness of medication use patterns, allowing users to self-assess their respiratory symptoms on a daily basis, sharing information on local environmental conditions, and producing user reports to review their data over time. The software consists of a smart device application compatible for iPhone operating systems (iOS) and Android operating systems that will store data locally on the patient's smart device. The App	Changed "respiratory disease" to "asthma and/or COPD" to be more specific. "Mobile" revised to" smart device" for consistency within the protocol. Type of data added. The smart device camera sentence was moved to this section from Section 5.1.2.2 for correctness.

Original text with changes shown	New wording	Reason/Justification for change
will allow the patient to track their usage of medication, inhalation results, and self-assessments related to their asthma or COPD ~~respiratory conditions~~. The App gets environment information from 1 or more web services.	will receive a patient's health data automatically from the inhaler devices via Bluetooth on a smart device. The smart device camera will be used for scanning and pairing. This data will allow the patient to track their usage of medication, inhalation results, and self-assessments related to their asthma or COPD. The App gets environment information from 1 or more web services.	
Section 5.1.2.2 Teva Digital Health Platform (Cloud Solution)		
The Teva DHP is a system that stores and transfers health data collected from the App ~~and the inhaler~~. The cloud solution automatically synchronizes with the App after ~~every~~ events ~~captured~~ and/or at predetermined time periods/intervals. An internet connection to the smart device (eg, ~~via~~ wireless or cellular phone network) is required in order for communication to be established between the App and the cloud solution. ~~The phone camera will be used for scanning and pairing.~~ The cloud solution will not send any notifications to the App. The cloud solution does not create, modify, or delete patient information. ~~By consenting to enrollment in the study and approving the privacy policy and terms of use, the patient accepts data synchronization with the cloud solution. If a patient does not provide consent to synchronize his/her App, no data will be transmitted to the cloud solution.~~ Patient privacy will be maintained according to the laws and regulations, and patient identifiers will be substituted to maintain a patient's ~~anonymity~~ privacy to reviewers of the data.	The Teva DHP is a system that stores and transfers health data collected from the App. The cloud solution automatically synchronizes with the App after events and/or at predetermined time periods/intervals. An internet connection to the smart device (eg, wireless or cellular phone network) is required in order for communication to be established between the App and the cloud solution. The cloud solution will not send any notifications to the App. The cloud solution does not create, modify, or delete patient information Patient privacy will be maintained according to the laws and regulations, and patient identifiers will be substituted to maintain a patient's privacy to reviewers of the data.	Paragraphs reordered and language revised for clarity. Deleted language in this section and new language added to Section 5.1.1 for better placement within the document.

Original text with changes shown	New wording	Reason/Justification for change
Section 5.1.2.3 Dashboard		
The data available on the dashboard are the inhaler data from the App and patient self-assessments. ~~, and environmental information received by the App. By default, data are not available on the dashboard (although stored on the cloud), unless the patient is required per the treatment group and gives consent to sharing of the data with the HCP in the informed consent.~~	The data available on the dashboard are the inhaler data from the App and patient self-assessments. The patient has no interaction with the dashboard. Teva personnel will have no access to the dashboard.	Environmental information included in error and now deleted. Deleted consent language and new language added to Section 5.1.1.
Section 5.2.1 Storage and Security (Other section affected by this change: Section 5.8)		
The investigational center personnel are responsible for acknowledging receipt of the IMP using ~~the interactive response technology~~ a Randomization and Trial Supply Management (RTSM) system.	The investigational center personnel are responsible for acknowledging receipt of the IMP using a Randomization and Trial Supply Management (RTSM) system.	Revised to make consistent with text used in the protocol.
Section 6.1.1 Asthma Control Test (Other sections affected by this change: Sections 6.1.2 and 6.1.3)		
The self-administered version of the ACT will be answered by the patients at the investigational center at Visit 1, ~~and~~ Visit 2, ~~and at any unscheduled visit~~ or at the Early Termination visit.	The self-administered version of the ACT will be answered by the patients at the investigational center at Visit 1, Visit 2, or at the Early Termination visit.	Corrected the visits when the questionnaires should be given to patients.
Section 6.1.4 System Usability Questionnaire		
The SUS will be answered by patients in the DS group, 18 years of age or older, at Visit 2, or at the ET visit. The SUS will be completed after all other questionnaires. A SUS will be completed by investigational center personnel, regarding the use of the dashboard, at the end of the study.	The SUS will be answered by patients in the DS group, 18 years of age or older, at Visit 2, or at the ET visit. The SUS will be completed after all other questionnaires. A SUS will be completed by investigational center personnel, regarding the use of the dashboard, at the end of the study.	Clarified when the SUS will be completed by patients and investigational center personnel.
Section 7.1.1 Definition of an Adverse Event		
A~~n asthma exacerbation~~ CAE will be defined by 1 of the following: ~~1) a reduction in FEV_1 of 20% or greater, 2)~~ 1) in-patient hospitalization because of asthma, ~~3~~2) emergency treatment because of asthma, or 43) use of prednisone or systemic	A CAE will be defined by 1 of the following: 1) in-patient hospitalization because of asthma, 2) emergency treatment because of asthma, 3) use of prednisone or systemic corticosteroids for 3	Moved contents of Section 7.1.7 to this section, deleted first paragraph, and reordered and corrected errors.

Original text with changes shown	New wording	Reason/Justification for change
corticosteroids for 3 days or more, or 4) a reduction in FEV_1 of 20% or greater~~,~~. Patients will be instructed to contact the study investigational center in the event of ~~an asthma exacerbation~~ CAE. All CAE events require documentation by the investigator in the CAE ~~Exacerbation~~ Page in the CRF, as well as in the adverse event CRF. All evaluations entered into the CAE ~~Exacerbation~~ Page require the investigational center to obtain source documentation of all ~~asthma exacerbations~~ CAEs that occur during the treatment period to confirm the accuracy of the information obtained from the patient.-Any CAE that meets serious adverse event criteria will be reported as a serious adverse event (Section 7.1.5.1). ~~The process for reporting a protocol-defined adverse event of special interest is the same as that for reporting a serious adverse event (Section 7.1.5.3). Protocol-defined adverse events of special interest are to be reported to GPSP and can be either serious or nonserious, according to the criteria outlined in Section 7.1.5.1.~~	days or more, or 4) a reduction in FEV_1 of 20% or greater. Patients will be instructed to contact the study investigational center in the event of a CAE. All CAE events require documentation by the investigator in the CAE Page in the CRF, as well as in the adverse event CRF. All evaluations entered into the CAE Page require the investigational center to obtain source documentation of all CAEs that occur during the treatment period to confirm the accuracy of the information obtained from the patient.-Any CAE that meets serious adverse event criteria will be reported as a serious adverse event (Section 7.1.5.1).	
Section 10.1 Sample Size and Power Considerations		
The recommended sample size for the study is 150 evaluable patients per group (~~10~~30 investigational centers, with each investigational center enrolling at least ~~15~~ 10 patients), 300 patients in total.	The recommended sample size for the study is 150 evaluable patients per group (30 investigational centers, with each investigational center enrolling at least 10 patients), 300 patients in total.	This change was made to correct the number of investigational centers and the number of patients to be enrolled at each investigational center.
Section 10.5.4.1 Primary Efficacy Analysis		
2. A binary distribution is assumed for the primary endpoint. Patients who discontinue early due to technology failure, disliking the digital platform, disease worsening, adverse experience or disliking the IMP will be counted as treatment failures. ~~Patients who discontinue early due to reasons not~~	2. A binary distribution is assumed for the primary endpoint. Patients who discontinue early due to technology failure, disliking the digital platform, disease worsening, adverse experience or disliking the IMP	The equation was changed because baseline ACT value is another factor we need to adjust assuming a correlation between change from baseline and baseline ACT scores.

Original text with changes shown	New wording	Reason/Justification for change
~~associated with these reasons will be assumed to have outcomes similar to others in their treatment group.~~ For those who discontinue early not due to these reasons, the ACT value assessed at the ET visit will be used. ~~3. Intercurrent events of withdrawal due to disliking technology, technology failure, disease worsening, adverse experiences, or disliking the IMP will be captured through definition of analysis set.~~ ~~4.~~3. Summary measure: A successful differentiation between the 2 groups will be determined by a Bayesian posterior probability for β_1 greater than 0.95 (1-sided). The following statistical methods will be utilized: Logistic regression model allowing for different response rates at enrolling investigational centers will be used for testing the hypothesis $H_0: \beta_1 = 0$, $H_1: \beta_1 > 0$ in the following model: $ln\frac{p_{ij}}{1-p_{ij}} = \delta_j + \beta_0 baseline\ ACT\ value \pm \beta_1 x_{ij}$ ~~Where *pij* denotes response proportion in each group for each investigational center.~~ Where i = treatment group, j = investigational center, x_{ij} = treatment group i for investigational center j, p_{ij} = response proportion of treatment group i in investigational center j.	will be counted as treatment failures For those who discontinue early not due to these reasons, the ACT value assessed at the ET visit will be used. 3. Summary measure: A successful differentiation between the 2 groups will be determined by a Bayesian posterior probability for β_1 greater than 0.95 (1-sided). The following statistical methods will be utilized: Logistic regression model allowing for different response rates at enrolling investigational centers will be used for testing the hypothesis $H_0: \beta_1 = 0$, $H_1: \beta_1 > 0$ in the following model: $ln\frac{p_{ij}}{1-p_{ij}} = \delta_j + \beta_0 baseline\ ACT\ value + \beta_1 x_{ij}$ Where i = treatment group, j = investigational center, x_{ij} = treatment group i for investigational center j, p_{ij} = response proportion of treatment group i in investigational center j.	Number 3 was deleted because it is no longer relevant since number 2 already covers all the reasons for early termination.
Section 10.5.4.3 Secondary Efficacy Analysis (Other section affected by this change: Section 10.7)		
For continuous variables, descriptive statistics (number [n], mean, standard deviation, median, minimum, and maximum) will be provided for ~~actual~~ observed values and changes from baseline to each time point.	For continuous variables, descriptive statistics (number [n], mean, standard deviation, median, minimum, and maximum) will be provided for observed values and changes from baseline to each time point.	Word changed for accuracy.

Original text with changes shown	New wording	Reason/Justification for change
Appendix A. Clinical Laboratories and Other Departments and Institutions		
[redacted] Teva Pharmaceuticals [redacted] Teva Pharmaceuticals [redacted]	[redacted] Teva Pharmaceuticals [redacted]	Change of Safety Physician.
Appendix B. Study Procedures and Assessments by Visit, 1. Procedures for Screening/Baseline Visit (Visit 1, Day 1)		
• administer pre-intervention Asthma Control Test (ACT) to all patients • administer Brief Medication Questionnaire (BMQ) and Brief Illness Perception Questionnaire (BIPQ) to patients 18 years of age or older • create and provide patient-specific unique email account to patients in the Digital System (DS) group for registration and onboarding in the application (App) • reimburse or dispense voucher to patients in the concurrent control (CC) group	• administer pre-intervention Asthma Control Test (ACT) to all patients • administer Brief Medication Questionnaire (BMQ) and Brief Illness Perception Questionnaire (BIPQ) to patients 18 years of age or older • create and provide patient-specific unique email account to patients in the Digital System (DS) group for registration and onboarding in the application (App) • reimburse or dispense voucher to patients in the concurrent control (CC) group	Text revised to match Table 3.

Original text with changes shown	New wording	Reason/Justification for change
Appendix B, Study Procedures and Assessments by Visit, 3. Procedures for End of Study/Early Termination Visit (Visit 2, Day 84 + up to 7 days)		
• iHCP asks Asthma Management questions • administer ACT to all patients and BMQ and BIPQ, to ~~all~~ patients, 18 years of age or older • administer System Usability Scale (SUS) to patients in the DS group, 18 years of age or older and investigational center personnel	• iHCP asks Asthma Management questions • administer ACT to all patients and BMQ and BIPQ, to patients, 18 years of age or older • administer System Usability Scales (SUS) to patients in the DS group, 18 years of age or older, and investigational center personnel	Text added to match text in Table 3.
Appendix B. Study Procedures and Assessments by Visit, 4. Unscheduled Visits or Phone Calls		
The following procedures and assessments will be performed at ~~Procedures performed during~~ unscheduled visits and unscheduled phone calls ~~include~~: • conduct~~ing~~ adverse events and adverse device effects inquiry • conduct~~ing~~ concomitant medication inquiry • record~~ing~~ reason for unscheduled visit or call • measure~~ing~~ vital signs (unscheduled visit only) • ~~ACT, BMQ, and BIPQ (unscheduled visit only)~~ • dispense~~ing~~ Albuterol eMDPI as needed (unscheduled visit only)	The following procedures and assessments will be performed at unscheduled visits and unscheduled phone calls: • conduct adverse events and adverse device effects inquiry • conduct concomitant medication inquiry • record reason for unscheduled visit or call • measure vital signs (unscheduled visit only) • dispense Albuterol eMDPI as needed	Text revised to match previous sections and to match Table 3

Original text with changes shown	New wording	Reason/Justification for change
• perform~~ing~~ Albuterol eMDPI collection and accountability (unscheduled visit only) • review~~ing~~ patient compliance • <u>iHCP asks Asthma management questions</u>	(unscheduled visit only) • perform Albuterol eMDPI collection and accountability (unscheduled visit only) • review patient compliance • iHCP asks Asthma management questions	
Appendix B, Study Procedures and Assessments by Visit, 5. Procedures for Follow-up Telephone Call (Day 98 + 7 days)		
	The following procedures and assessments will be performed at the follow-up telephone call: • conduct adverse events and adverse device effects inquiry • conduct concomitant medication inquiry • confirm that the patient has returned to previous asthma treatment	Text added to match text in Table 3.

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted] Global Medical Affairs, Teva Pharmaceuticals [redacted]
Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study	[redacted] Global Medical Affairs, 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	[redacted]

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

1. **Procedures for Screening/Baseline Visit (Visit 1, Day 1)[2]**

The following procedures and assessments will be performed at Visit 1:

- obtain written informed consent/assent
- review inclusion and exclusion criteria
- obtain medical history
- obtain current medication and treatment history related to asthma
- measure vital signs
- conduct adverse events and adverse device effects inquiry
- inform patients of study restrictions and compliance requirements
- administer pre-intervention Asthma Control Test (ACT) to all patients
- administer Beliefs about Medicines Questionnaire (BMQ) and Brief Illness Perception Questionnaire (BIPQ) to patients 18 years of age or older
- randomize and assign patient number
- create and provide patient-specific unique email account to patients in the Digital System (DS) group for registration and onboarding in the application (App)
- train patients in the DS group on use and proper technique of the albuterol multidose dry powder inhaler with integrated electronic module (Albuterol eMDPI)
- dispense Albuterol eMDPI to patients in the DS group
- reimburse or dispense voucher to patients in the concurrent control (CC) group

2. **Procedures for Treatment Period (Day 1 through Day 84)**

The following procedures and assessments will be performed during the Treatment Period:

- resupply Albuterol eMDPI, if necessary

3. **Procedures for End of Treatment/Early Termination Visit (Visit 2, Day 84 + up to 7 days)**

The following procedures and assessments will be performed at Visit 2:

- conduct adverse events and adverse device effects inquiry
- conduct concomitant medication inquiry
- measure vital signs
- iHCP asks Asthma Management questions

[2] Patients may be enrolled up to 7 days after screening.

- administer ACT to all patients and BMQ and BIPQ, to patients, 18 years of age or older
- administer System Usability Scale (SUS) to patients in the DS group, 18 years of age or older, and investigational center personnel
- perform Albuterol eMDPI collection and accountability
- remove the App from the patient's smart device

4. **Procedures for Clinically Driven Assessment(s) (If Necessary)**

A Clinically Driven Assessment, which can either be via telephone or an on-site visit, may be performed at any time during the study at the patient's request and as deemed necessary by the investigator. For DS patients, the investigator will have access to information from the Albuterol eMDPI on the patient's SABA use and inhalation technique through the dashboard. If the investigator meets with or calls the patient as a result of an interaction with the dashboard, this will be captured as a Clinically Driven Assessment.

The date and reason for the Clinically Driven Assessment (eg, treatment step up, treatment step down, adherence discussion, treatment for an asthma exacerbation, or other clinical encounters generated by the data from the Albuterol eMDPI), as well as any other data obtained from procedures and assessments, will be recorded in the patient's source documents and the case report form (CRF) for patients in both groups, during the 12-week treatment period.

The following procedures and assessments will be performed at a Clinically Driven Assessment:

- conduct adverse events and adverse device effects inquiry
- conduct concomitant medication inquiry
- iHCP asks Asthma Management questions
- dispense Albuterol eMDPI, as needed (if on-site and necessary)

Other procedures and assessments may be performed at the discretion of the investigator.

5. **Procedures for an Unscheduled Investigational Medicinal Product Dispensing Visit**

The following procedures and assessments will be performed at an unscheduled IMP dispensing visit:

- conduct adverse events and adverse device effects inquiry
- conduct concomitant medication inquiry
- perform Albuterol eMDPI collection and accountability
- dispense test investigational medicinal product (IMP) to DS group patients

6. **Procedures for Follow-up Telephone Call (Day 98 + 7 days)**

The following procedures and assessments will be performed at the follow-up telephone call:

- conduct adverse events and adverse device effects inquiry

- conduct concomitant medication inquiry
- for DS group patients, confirm that the patient has returned to previous asthma treatment

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/Institutional Review Board (IEC/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 Deviations

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

When a protocol deviation is reported, the sponsor will determine whether to withdraw 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 investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol deviation. 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 (ICF) 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(s) are to visit the investigator before, during, and after the study to ensure that there is 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(s) 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 documents 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.

In case of an emergency situation (eg, the COVID-19 pandemic), where study monitors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with local regulations.

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.

In case of an emergency situation (eg, the COVID-19 pandemic), where auditors may not be able to access the investigational centers for on-site visits, investigational centers will be monitored remotely, where allowed, and in accordance with local regulations.

APPENDIX D. ETHICS

Informed Consent/Assent

For patients ≥18 years of age, 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 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 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.

For patients ages ≥13 to <18 years of age, 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 ICF 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. 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, 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 F. PRODUCT COMPLAINTS

I. Clinical Product Complaints/Device Deficiency

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 clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue.

For complaints involving a device/combination product or other retrievable item, it is required that the device/combination product (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.

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.

Handling of Investigational Medicinal Product(s) and Devices 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 or devices, the sponsor will provide the information needed to handle the return.

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, if applicable.

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).

Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, the initial determination whether the deficiency could have led to a serious adverse event (Section II), 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.

II. Assessment of Device Performance

Device performance will be assessed by device deficiencies and product complaints.

A device deficiency is defined as any inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety, or performance (Appendix Figure 1). This definition includes malfunctions, use errors, inadequate labeling (eg, unintelligible label, incorrect expiry date), and product complaints that are related to the eMDPI.

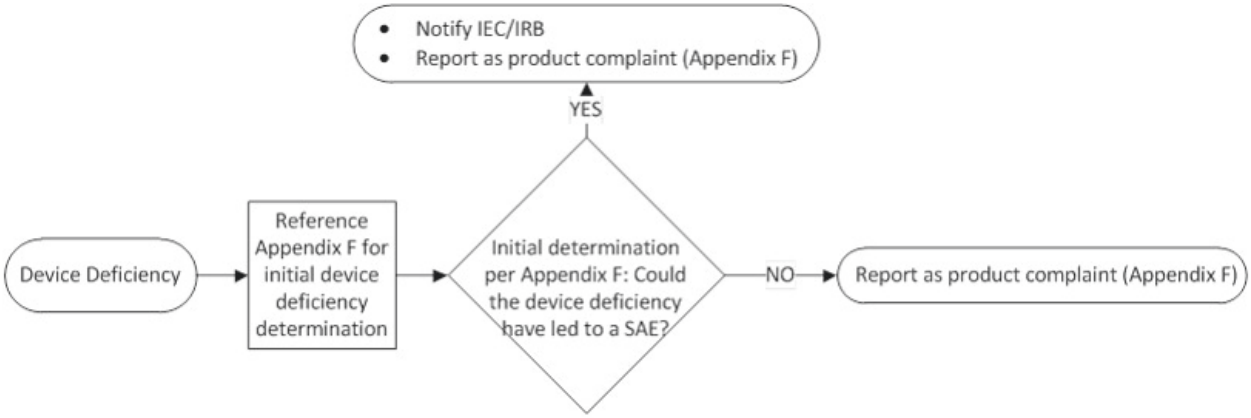
The investigator should use Appendix Table 1 and Appendix Table 2 to help make an initial determination whether the device deficiency could have led to a serious adverse event and notify

the sponsor by completing the product complaint form provided by Teva and emailing it to clinical.productcomplaints@tevapharm.com.

Device deficiencies with potential serious adverse device effect are defined as deficiencies that might have led to a serious adverse device effect if (Appendix Figure 1):

- suitable action had not been taken (or)
- intervention had not been made (or)
- circumstances had been less fortunate

Appendix Figure 1: Decision Tree for Device Deficiencies



IEC=Independent Ethics Committee; IRB=Institutional Review Board; SAE=serious adverse event.

Appendix Table 1: Potential Use-Related Deficiencies That Could Lead to Serious Adverse Events

Use Step	Use Error	Potential Hazard Situation	Potential Harm
Setup App (first use)	User thinks they need to use App to use inhaler	Continuous use - no dose	Worsening of condition
Preparing the inhaler	User opens cap with inhaler in upside down position/ User does not apply directional force to open cap	Continuous use - no dose	Worsening of condition
Inhalation	User does not understand the importance of not breathing into the inhaler / User does not realize inhaler is breath activated	Continuous use - no dose	Worsening of condition
Close cap after use	User does not apply directional force to close cap	Continuous use - no dose	Worsening of condition
End of life	User continues using inhaler when 0 inhalations remaining	Continuous use - no dose	Worsening of condition
Cleaning	User washes device in water	Continuous use - no dose	Worsening of condition

Appendix Table 2: Potential Design-Related Deficiencies That Could Lead to Serious Adverse Events

Device Component	Failure Mode	Potential Hazard Situation	Potential Harm
Dose counter	Undercounting, dose counter displays doses remaining after the inhaler has dispensed 200 doses	Continuous use - no dose	Worsening of condition
Dustcap	Dustcap broken/ detached/misaligned	Continuous use - no dose	Worsening of condition
Other internal components	Drug not delivered	Continuous use - no dose	Worsening of condition

Appendix G. 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 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 (eg, clinical laboratory, central image center, or electronic diary data), 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, IEC/IRB, and inspectors from competent authorities (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 (US) 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 (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, electronic patient-reported outcome [ePRO] tablet), 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 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, national and local laws, including, but not limited to:

- full case histories
- signed ICFs
- 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, electronic diary)
- 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 the 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 H. 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" (International Committee of Medical Journal Editors [ICMJE] Recommendations 2017). 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 ICMJE 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.