Clinical Study Protocol

CONNected Electronic Inhalers Asthma Control Trial 2 ("CONNECT 2"), a 24-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study of Standard of Care Treatment Versus the eMDPI Digital System, to Optimize Outcomes in Patients at Least 13 Years of Age or Older with Asthma

Study Number FSS-AS-40139

NCT04677959

Protocol with Amendment 01 Approval Date: 19 April 2021

Clinical Study Protocol with Amendment 01

Study Number FSS-AS-40139

CONNected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 2 ("CONNECT 2"), a 24-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study of Standard of Care Treatment Versus the eMDPI Digital System, to Optimize Outcomes in Patients at Least 13 Years of Age or Older with Asthma

Short title: A 24-Week Treatment Study to Compare Standard of Care Versus the eMDPI DS in Patients 13 Years or Older with Asthma

Lay person title**:** A Study to Test if Using the 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 numbers: 072240, 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: 30 August 2020

Protocol with Amendment 01 Approval Date: 19 April 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 FSS-AS-40139 (original protocol dated 30 August 2020) has been amended and reissued as follows:

Amendment 01	19 April 2021 34 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 30 August 2020

Protocol with Amendment 01 Approval Date: 19 April 2021

IND numbers: 072240, 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 01 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 30 August 2020

Protocol with Amendment 01 Approval Date: 19 April 2021

IND numbers: 072240, 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

CONNected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 2 ("CONNECT 2"), a 24-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study of Standard of Care Treatment Versus the 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 01 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 01

Study Number FSS-AS-40139

Title of Study: CONNected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 2 ("CONNECT 2"), a 24-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study of Standard of Care Treatment Versus the 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) Numbers: 072240, 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 Products (IMPs):

- Fluticasone propionate/salmeterol (FS) electronic multidose dry powder inhaler (eMDPI) Digital System (DS) with 4 component devices:
  - Device 1: FS eMDPI
  - Device 2: Patient-facing smart device application (App, same for both IMPs)
  - Device 3: Digital Health Platform (DHP) (Cloud solution, same for both IMPs)
  - Device 4: Provider-facing dashboard (same for both IMPs)
- Albuterol electronic eMDPI DS with 4 component devices:
  - Device 1: Albuterol eMDPI
  - Device 2: Patient-facing smart device App (same for both IMPs)
  - Device 3: DHP (Cloud solution, same for both IMPs)
  - Device 4: Provider-facing dashboard (same for both IMPs)

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

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

Indications:

FS eMDPI: treatment of asthma in patients aged 12 years or older

Albuterol eMDPI: 1) Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway 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 45 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 Q1 2021 and last until approximately Q2 2022.

Number of Patients Planned (total): A total of approximately 388 patients will be enrolled in the study (accounting for 10% early dropouts) and the number of evaluable patients is planned to be 350, 200 patients in the DS group and 150 patients in the Standard of Care (SoC) group.

Study Population: The study population will consist of patients 13 years of age or older with a diagnosis of asthma, currently on a moderate- to high-dose inhaled corticosteroid (ICS) with a long-acting beta$_2$ agonist (LABA), with 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 the SoC group.	The primary endpoint is the proportion of patients for the DS and SoC groups achieving 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 ACT units from baseline at the end of the 24-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 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 long-acting muscarinic antagonist (LAMA) or

Objectives	Endpoints
	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 24-week treatment period for the DS group.
The secondary objective (#3) is to evaluate adherence patterns to maintenance treatment (FS eMDPI) in the DS group.	This secondary endpoint is the change from baseline in adherence to maintenance treatment (FS eMDPI), defined as the proportion of actual inhalation doses taken out of the total number of inhalation doses prescribed over the 24-week treatment period.
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 SoC 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 work productivity and activity impairment in asthma patients in both groups.	This secondary endpoint is the change from baseline measured by the Work Productivity and Activity Impairment (WPAI) questionnaire, completed by patients 18 years of age or older in both groups, at baseline and at the end of the 24-week treatment period.
The **secondary objective (#6)** 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 (#7)** is to evaluate the safety of FS eMDPI and Albuterol eMDPI.	This secondary endpoint is the reporting of adverse events related to FS eMDPI and Albuterol eMDPI at participating investigational centers. The safety endpoints for this study include the following for all patients in both groups:

Objectives	Endpoints
	• adverse event data • adverse device effect data

Notes: The Digital System (DS) group will include eligible study population patients who will use the DS (FS eMDPI, Albuterol eMDPI, and common App, DHP [cloud solution], and dashboard) during the treatment period. The Standard of Care (SoC) group will include eligible patients who will be treated with their current treatment provided by the investigational center to the patient, based on asthma guidelines.

[redacted]

General Study Design:

This is a 24-week treatment, multicenter, open-label, randomized, parallel group comparison feasibility study of SoC treatment versus the using the 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 24-week, open-label treatment period with Visit 2 (either in-person or remote) at Week 12 and Visit 3 at Week 24, and a follow-up telephone call (2 weeks following treatment completion or early termination).

Patients with suboptimal asthma control will be enrolled in the study and randomized, in a 4:3 ratio, respectively, to 1 of 2 parallel groups (Table 2). The randomization will be stratified by investigational center.

Table 2: Description of Treatment Groups

DS group	SoC group
FS eMDPI[a] + App	Current ICS/LABA and any additional controller medication for asthma (except for biologics)
Albuterol eMDPI + App	Current rescue medication
DHP (Cloud solution)	Not applicable
Provider-facing dashboard	Not applicable

[a] iHCP can add another controller medication other than an ICS with LABA, including a biologic, to the DS patient's treatment, if needed.
Albuterol eMDPI=Albuterol electronic multidose dry powder inhaler; App=smart device application; DHP=Digital Health Platform; DS=Digital System; FS eMDPI=fluticasone propionate/salmeterol electronic multidose dry powder inhaler; ICS=inhaled corticosteroid; iHCP=investigational center health care provider; LABA=long-acting beta$_2$ agonist.

The DS group patients will use the FS eMDPI and the Albuterol eMDPI with a common App, DHP (Cloud solution), and dashboard. The SoC group patients, who will include eligible patients treated with their current treatment provided by the investigational center to the patient, based on asthma guidelines, will not use the DS during the treatment period. Similar data will be collected regarding outcomes for both groups: ACT after 24 weeks, BMQ, BIPQ, Mini-AQLQ, and WPAI questionnaire responses, and the frequency of CAEs.

All patients will have a screening/baseline visit (Visit 1), at which they will be asked if they own a smart device and use different applications on their smartphones. A baseline ACT score for all patients and BMQ, BIPQ, Mini-AQLQ, and WPAI questionnaire responses, for patients 18 years of age or older, will be collected. At Visit 1, patients in the DS group will be trained on the use of the eMDPI (including instructions on how to use both the eMDPIs and the App). Upon demonstrating competency, patients in the DS group will have their maintenance ICS with LABA switched to the FS eMDPI (at a dose of fluticasone comparable to their most recent current ICS dose) and their rescue treatment switched to the Albuterol eMDPI. All other asthma maintenance medications, except for ICS with LABA, may be continued. The iHCP can add another controller medication other than an ICS with LABA, including a biologic, to the DS patient's treatment, if needed. Patients in the SoC group will be reimbursed or given a voucher to use to purchase their existing maintenance ICS with LABA and rescue medications. Patients in the DS group will receive a new FS eMDPI device at Visit 1 and 1 FS eMDPI device and 1 Albuterol eMDPI device at Visit 2. Periodically after Visits 1 and 2, patients will be shipped a new FS eMDPI device, which they will need to pair with the App. The patient will immediately stop using the old device and switch to the new device. Extra Albuterol eMDPI devices may be shipped as needed, based on the clinical judgment of the investigator. Upon receipt, the patient will pair the new device with the App and will immediately stop using the old device and switch to the new device. To trigger direct-to-patient (DTP) shipments, after Visit 1, the investigational center will receive periodic email reminders to access the interactive response technology (IRT) system to confirm the dose of test IMP to be shipped to the patient. Confirmation of the dose is required before the next shipment can be sent.

Investigational centers will receive similar instruction regarding features of the App, as well as features of the associated common dashboard, which mirrors the digital information obtained

from the eMDPIs and the App, including frequency and times of SABA rescue use and associated inspiratory flow parameters measured by the eMDPI with each inhalation.

The SoC group will be followed according to the clinical judgment of the investigator; the asthma of patients in the SoC group will be managed in a manner consistent with the clinical judgement of the investigator and based on asthma management guidelines (eg, Global Initiative for Asthma). Similar to the management of the SoC group, the DS group patients will be followed by the investigational centers with the addition of objective information on FS eMDPI and 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, along with any other additional information about the patient, as per their clinical judgement, to modify patients' asthma management. The investigator may, if indicated, modify the patient's regime, including adding asthma controllers or biologics as otherwise clinically indicated in the judgement of the investigator. 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, Visit 3, and any 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.

Visit 2 (if it is an in-person visit) will include dispensing of new inhalers to the DS group patients and return of used or unused inhalers that were dispensed to the patients previously. New FS eMDPI devices will continue to be shipped directly to patients periodically after Visit 2 until the end of treatment. The ACT will be completed and scores registered.

At the end of the treatment period (24 weeks), final assessments of the DS and SoC groups will be completed, as specified in Table 5, and the rest of the inhalers that were dispensed to the DS group patients will be returned. A follow-up telephone call will be made by the investigational center to all patients, 2 weeks later, and will confirm that the DS group patients have returned to their 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.

Method of Randomization and Blinding:

Patients will be randomly assigned to the DS group or SoC group in a 4:3 ratio, stratified by investigational center, respectively, using a Randomization and Trial Supply Management system.

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

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

Test IMPs:

- FS eMDPI DS with 4 component devices:
  - Device 1: FS eMDPI
  - Device 2: Patient-facing smart device App (same for both IMPs)
  - Device 3: DHP (Cloud solution, same for both IMPs)
  - Device 4: Provider-facing dashboard (same for both IMPs)
- Albuterol eMDPI DS with 4 component devices:
  - Device 1: Albuterol eMDPI
  - Device 2: Patient-facing smart device App (same for both IMPs)
  - Device 3: DHP (Cloud solution, same for both IMPs)
  - Device 4: Provider-facing dashboard (same for both IMPs)

Reference IMP:

- SoC asthma medications

Placebo IMP: none

Investigational medicinal products are defined as the test IMP, reference IMP, and placebo IMP (Table 3).

Table 3: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Test IMP	Placebo IMP	Reference IMP
Trade name and INN, if applicable, or company-assigned number	FS eMDPI	Albuterol eMDPI	None	SoC asthma medications
Formulation	Inhalation powder	Inhalation powder	NA	Inhalation aerosol and/or inhalation powder
Unit dose strength(s)/Dosage level(s)	fluticasone propionate/salmeterol inhalation powder, 113 mcg/14 mcg 232 mcg/14 mcg	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	Oral inhalation	NA	Oral inhalation
Dosing instructions/Dosing schedule/Titration periods/Treatment periods	1 inhalation, twice daily	1 to 2 inhalations every 4 to 6 hours, as needed	NA	NA
Packaging	NA	NA	NA	NA
Manufacturer	Teva Pharmaceutical Industries, Ltd. Jerusalem, Israel, or Teva Pharmaceuticals Ireland, Waterford, Ireland	Teva Pharmaceutical Industries, Ltd. Jerusalem, Israel, or Teva Pharmaceuticals Ireland, Waterford, Ireland	NA	NA

Albuterol eMDPI=Albuterol sulfate electronic multidose dry powder inhaler; FS eMDPI=fluticasone propionate/salmeterol electronic multidose inhaler; IMP=investigational medicinal product; INN=International Nonproprietary Name; NA=not applicable; SoC=Standard of Care.

Duration of Patient Participation and Maximal Exposure to IMP: The total duration of patient participation in the study is planned to be 26 weeks.

Study Duration: Approximately 15 months (from Q1 2021 to Q2 2022)

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 asthma medications at treatment end and follow up through their HCPs.

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 a moderate- to high-dose ICS with LABA.

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

e. The patient is willing to discontinue all other maintenance ICS with LABA medications and rescue medications and replace them with the study-provided FS eMDPI and Albuterol eMDPI, respectively, for the duration of the trial, if randomized to the DS group. All other asthma maintenance medications, except for ICS with LABA, may be continued.

f. 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. [Revision 1] 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.

b. 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.

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

d. 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.

e. The patient has a diagnosis of chronic obstructive pulmonary disease (COPD) or asthma-COPD overlap (ACO).

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

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

h. 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 judgement of the investigator as part of their asthma management and remain in the study.)

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

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:

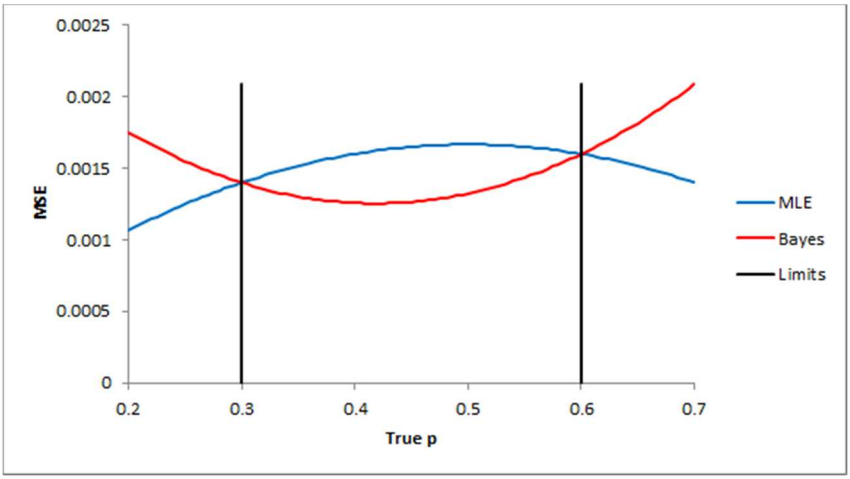
The sample size was selected based on a Bayesian approach which allows for a range of underlying proportions rather than a fixed predefined value.

A total of 388 patients will be enrolled in the study (accounting for 10% early dropouts), 200 patients in the DS group and 150 patients in the SoC group, to be available for analysis. The sample size determination was made assuming binomial distribution for the primary endpoint. An informative prior the for SoC group (Beta [9.52, 11.88]) was selected to reflect the belief that the response rate of the SoC group is between 30% and 60% (most likely 45%, Merchant 2016) and the effect size between groups of 13% difference in response rates was considered clinically meaningful.

In addition, an informative prior for the SoC group was selected to ensure that the mean square error for the Bayes estimate from the informative prior is superior to the maximum likelihood estimate over a range of 30% and 60% of anticipated proportion for SoC group.

It should be noted that both power and Type 1 error are dependent on the absolute difference between the DS and the SoC 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



MLE=maximum likelihood estimation; MSE=mean squared error

A non-informative prior (Beta [0.5,0.5]) for the DS group was selected due to lack of availability of data in the DS group.

With assumptions of response rates of 58% and 45% for the DS and SoC groups, respectively, sample size and randomization ratio, the probability of the posterior odds ratio (OR) of improvement (ie, OR>1) for the DS group versus the SoC group of at least 0.95 is about 82%. This will ensure a 1-sided 5% Type 1 error rate and 78% power for an effect size for 13% difference between the groups provided that the proportion of responders in the SoC group is 45%.

Analysis Sets

Intent-to-Treat Analysis Set (ITT): The 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 mITT analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP (IMP is either FS eMDPI or Albuterol eMDPI for the DS group, or SoC medication for the SoC group) and at least 1 postbaseline assessment on any of the study endpoints.

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, [redacted] endpoint analyses.

Safety Analysis Set: The safety analysis set will include all patients in the DS group who receive at least 1 dose of IMP and all patients in the SoC 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 achieving 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 ACT units from baseline at the end of the 24-week treatment period (ie, a responder is defined by an ACT score of greater than or equal to 20 or an increase of greater than or equal to 3 ACT units from baseline).

The analysis is set within an estimand framework that will address objectives of the study, the effectiveness of the DS, specifically: is there a difference in treatment groups in the number of patients achieving meaningful clinical asthma control. Withdrawals due to technology failure, disliking technology, or disliking IMP will be counted as nonresponders.

Estimand framework:

1. Population: The patients met all of the inclusion criteria and none of the exclusion criteria. The mITT analysis set will be the primary analysis set for the primary endpoint.
2. Variable: The primary endpoint will be a binary response variable at Week 24. A patient will be defined as a responder if the patient achieves an ACT score of greater than or equal to 20 or an increase of greater than or equal to 3 ACT units from baseline to Week 24. Otherwise, the patient will be defined as a nonresponder.
3. Intercurrent events: Treatment discontinuation due to an adverse event, lack of efficacy, technology failure, disliking the DS, disliking IMP, or other reasons. For those who discontinue the treatment before Week 24, no further data will be collected.
4. Population-level summary: The primary endpoint will be analyzed using a logistic model, where binary variable responder rate (Yes/No) will be modeled through logit link function, with baseline ACT score and treatment as explanatory factors. For those who discontinue the treatment before Week 24 due to technology failure, disliking the DS, or disliking IMP, the patients will be defined as nonresponders; for those who discontinue early not due to these reasons, the response at the Early Termination visit will be used. The mean and 95% credible intervals of the response rates and OR from the posterior distributions will be calculated and presented. An informative prior will be assumed for the model coefficient for treatment and non-informative priors will be assumed for all other model coefficients. The details for the data analysis will be specified in the Statistical Analysis Plan.

Sensitivity Analysis:

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

Secondary Analysis:

Summaries of all secondary endpoints will be presented descriptively based on the mITT analysis set.

For continuous variables, descriptive statistics (number [n], mean, standard deviation [SD], 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.

[redacted]

Multiple Comparisons and Multiplicity:

No adjustments 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 5.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility) (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, SD, 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: No interim analyses are planned.

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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
BMQ	Beliefs about Medicines Questionnaire
BMQ-S11	Beliefs about Medicines Questionnaire-Specific
CAE	clinical asthma exacerbation
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
DTP	direct-to-patient
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
FP	fluticasone propionate
FS	fluticasone propionate/salmeterol
FS eMDPI	fluticasone propionate/salmeterol electronic multidose dry powder inhaler
FS MDPI	fluticasone propionate/salmeterol multidose dry powder inhaler
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GINA	Global Initiative for Asthma

GPSP	Global Patient Safety and Pharmacovigilance
HCP	healthcare provider
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroid
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
IRT	interactive response technology
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
MedDRA	Medical Dictionary for Regulatory Activities
Mini-AQLQ	Mini Asthma Quality of Life Questionnaire
mITT	modified intent-to-treat
NDA	New Drug Application
OR	odds ratio
PRO	patient-reported outcome
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
SABA	short-acting $beta_2$ agonists
SD	standard deviation
SoC	Standard of Care
SOP	Standard Operating Procedure
SUS	System Usability Scale
SUSAR	suspected unexpected serious adverse reaction

Sx	salmeterol xinafoate
US(A)	United States (of America)
WHO	World Health Organization
WHO Drug	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment

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] 2020).

Clinical data demonstrate that use of the fluticasone propionate/salmeterol (FS) combination in both adults and children with persistent asthma provides greater improvement in pulmonary function and overall asthma control than either individual component alone. The use of such a combination is recommended for the maintenance treatment of asthma in children, adolescents, and adults who remain symptomatic despite low-to-medium doses of an inhaled corticosteroid (ICS) in accordance with current guidelines for the management of asthma (National Asthma Education and Prevention Program [NAEPP] 2007).

Fluticasone propionate (Fp) is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. Inflammation is an important component of the pathophysiology of asthma and corticosteroids have been shown to inhibit multiple inflammatory cells and mediators involved in the pathophysiology of asthma. Salmeterol xinafoate (Sx) is a selective, long-acting beta$_2$ agonist (LABA). In vitro studies show salmeterol to be at least 50 times more selective for β_2-adrenoceptors than albuterol. The pharmacologic effects of β_2-adrenoceptor agonist drugs, including salmeterol, are at least in part attributable to stimulation of intracellular adenyl cyclase that leads to increased levels of cyclic-3′, 5′-adenosine monophosphate (AMP) leading to relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Teva Branded Pharmaceutical Products R&D, Inc. (Teva) has developed a combination product of Fp/Sx inhalation powders, using the Teva proprietary multidose dry powder inhaler (MDPI). The combination product, fluticasone propionate/salmeterol multidose dry powder inhaler (FS MDPI), is supplied in multiple dosage strengths of Fp with a fixed dosage of Sx (the conversion factor from Sx to salmeterol free base [Sb] is 0.6883). Salmeterol xinafoate will dissolve and dissociate into Sb (active moiety) in the lung to exert a therapeutic effect.

Teva has developed multiple dosage strengths of FS MDPI in order to allow treatment of the entire spectrum of persistent asthma. The Teva device-formulation combination allows for the concentrations of the drug in the formulation to be significantly lower than those in ADVAIR DISKUS® (GlaxoSmithKline) while achieving similar to lower systemic exposure and comparable clinical benefits.

The FS MDPI is formulated in lactose and delivers drug to the airways as a fine powder without the use of propellants. The FS MDPI is an inhalation-driven device and thus eliminates the need for coordination of actuation and inspiration.

On 27 January 2017, the United States (US) Food and Drug Administration (FDA) approved FS MDPI as AIRDUO RESPICLICK® (FS inhalation powder) for the treatment of asthma in patients 12 years of age or older. The approved metered dose strengths of AIRDUO RESPICLICK are 55/14 mcg, 113/14 mcg, and 232/14 mcg.

On 12 July 2019, the US FDA approved FS MDPI with an integrated electronic inhaler (eMDPI) as AIRDUO® DIGIHALER™ (FS) inhalation powder, for the same indication and metered dose strengths, supported by the same clinical development program as AIRDUO RESPICLICK (which does not contain the electronic module [eModule]). AIRDUO DIGIHALER contains a built-in eModule (ie, the Digihaler) that detects, records, and stores data on inhaler events for transmission to a smart device application (App). More detailed prescribing information for this product may be found in the FS eMDPI Investigator's Brochure (IB).

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, 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 (albuterol sulfate inhalation powder) has been available in the 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 (EIB) 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), delivering 90 mcg of albuterol base per actuation, for the same indication as PROAIR RESPICLICK. PROAIR DIGIHALER also contains the eModule (ie, the Digihaler) that detects, records, and stores data on inhaler events for transmission to a mobile App. More detailed prescribing information for this product may be found in the Albuterol eMDPI IB.

In this study, both FS (as maintenance medication) and albuterol sulfate (as rescue medication) will be delivered via an eMDPI. 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 a common Digital Health Platform (DHP; Cloud solution) and then to a common provider-facing dashboard. The DHP is used to provide patient-specific data to the patient's healthcare provider (HCP) via the dashboard, a secure web interface. The following devices will be evaluated in this study:

- FS eMDPI DS with 4 component devices:
  - Device 1: FS eMDPI
  - Device 2: Patient-facing smart device App (same for both investigational medicinal products [IMPs])
  - Device 3: DHP (Cloud solution, same for both IMPs)
  - Device 4: Provider-facing dashboard (same for both IMPs)
- Albuterol eMDPI DS with 4 component devices:
  - Device 1: Albuterol eMDPI
  - Device 2: Patient-facing smart device App (same for both IMPs)
  - Device 3: DHP (Cloud solution, same for both IMPs)
  - Device 4: Provider-facing dashboard (same for both IMPs)

The purpose of the study is to evaluate whether outcomes for patients using the FS eMDPI and Albuterol eMDPI DS can be optimized better than a Standard of Care (SoC) group who will be treated with their current treatment provided by the investigational center, based on asthma guidelines, 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, adherence patterns to maintenance treatment (FS eMDPI) in the DS group, 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

1.2.1. Studies with FS MDPI/FS eMDPI

A global clinical development program was conducted to evaluate the safety and efficacy of FS MDPI in adult and adolescent patients (12 years of age and older) with asthma. This clinical development program comprised 9 studies. Seven of the 9 studies included patients 12 years of age or older with persistent asthma. The other 2 studies (both Phase 1 pharmacokinetics studies)

included healthy adult subjects. This global clinical development program also supported the approval of FS eMDPI.

Overall, the data generated during the clinical development program supports the use of FS MDPI/FS eMDPI for the maintenance treatment of asthma in patients aged 12 years and older. Efficacy results of the Phase 2 and Phase 3 studies indicated that all 3 dose strengths of FS MDPI (metered doses 55/14, 113/14, and 232/14 mcg twice daily) significantly improve lung function, reduce rescue bronchodilator use, and improve asthma symptoms and quality of life in patients with asthma 12 years of age and older.

FS MDPI/FS eMDPI demonstrated a favorable safety profile in the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

Teva has also conducted a pediatric clinical development program for these products. This program consisted of a pharmacokinetics study (FSS-PK-10007) followed by a Phase 3 study (FSS-AS-30003) of the safety and efficacy of Fp MDPI in patients with asthma aged 4 to 11 years of age over a 12-week treatment period. Likewise, the Phase 3 pediatric efficacy study showed that treatment with Fp MDPI 25 and 50 mcg was associated with greater improvements in lung function (compared to placebo treatment) in children ages 4 through 11 years with persistent asthma.

More detailed information is provided in the FS eMDPI IB.

1.2.2. Studies with Albuterol MDPI/eMDPI

A comprehensive clinical development program was conducted in the US to evaluate the safety and efficacy of Albuterol MDPI/eMDPI in adult and adolescent patients (12 years of age and older) with asthma and EIB. It was comprised of one Phase 1 study in adults 18 through 45 years, one Phase 2 study in patients 12 years of age or older, and 5 Phase 3 studies in patients 12 years of age or older. A separate clinical development program was conducted in pediatric patients (4 through 11 years of age) to examine efficacy and safety of Albuterol MDPI in pediatric patients.

Overall, this clinical development program confirmed that Albuterol MDPI/eMDPI is an effective and well-tolerated therapy for the treatment and prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. Results showed that Albuterol MDPI has a comparable pharmacodynamic and efficacy profile to PROAIR HFA. Results also supported the effectiveness of Albuterol MDPI/eMDPI in the prevention of EIB. In addition, the comparable exposure of Albuterol MDPI relative to PROAIR HFA further established the expected safety profile as being consistent with that of PROAIR HFA, which has extensive postmarketing experience.

More detailed information is provided in the Albuterol eMDPI 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 FS eMDPI DS and the Albuterol eMDPI DS can be optimized better than a SoC group who will be

treated with their own current treatments and will not use the DS during the treatment period. In addition to assessing the technical reliability experienced by patients using the DSs, the study also uses 4 patient questionnaires, the Beliefs about Medicines Questionnaire (BMQ), the Brief Illness Perception Questionnaire (BIPQ), the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ), and the Work Productivity and Activity Impairment (WPAI) Questionnaire, for patients in both groups, 18 years of age or older, 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.

The FS eMDPI is a maintenance agent. Albuterol eMDPI is a rescue/reliever agent. The FS eMDPI DS consists of the FS eMDPI, the App, the Cloud solution, and the dashboard. The Albuterol eMDPI DS consists of the Albuterol eMDPI, the App, the Cloud solution, and the dashboard. The App, the Cloud solution, and dashboard are common to both DSs. Both eMDPIs 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 sources in the eMDPIs are fully integrated into the inhalers and are designed to operate for the life of the inhalers without intervention. The eModules record timestamped pre-defined events. The inclusion of the eModules has been shown to have no impact on the dose delivery compared with the approved products without the eModules (performance and functional testing on file at Teva). Additional information regarding benefits and risks of FS eMDPI and Albuterol eMDPI to patients may be found in the IBs.

In summary, the benefit and risk assessments for FS eMDPI and Albuterol eMDPI are 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 the SoC group.	The primary endpoint is the proportion of patients for the DS and SoC groups achieving well-controlled asthma as defined by an Asthma Control Test (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 ACT units from baseline at the end of the 24-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 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 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 24-week treatment period for the DS group.

Objectives	Endpoints
The secondary objective (#3) is to evaluate adherence patterns to maintenance treatment (FS eMDPI) in the DS group.	This secondary endpoint is the change from baseline in adherence to maintenance treatment (FS eMDPI), defined as the proportion of actual inhalation doses taken out of the total number of inhalation doses prescribed over the 24-week treatment period.
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 SoC 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 work productivity and activity impairment in asthma patients in both groups.	This secondary endpoint is the change from baseline measured by the WPAI questionnaire, completed by patients 18 years of age or older in both groups, at baseline and at the end of the 24-week treatment period.
The **secondary objective (#6)** 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 (#7)** is to evaluate the safety of FS eMDPI and Albuterol eMDPI.	This secondary endpoint is the reporting of adverse events related to FS eMDPI and 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 (FS eMDPI, Albuterol eMDPI, and common App, DHP [cloud solution], and dashboard) during the treatment period. The Standard of Care (SoC) group will include eligible patients who will be treated with their current treatment provided by the investigational center to the patient, based on asthma guidelines.

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 Institutes of Health as a 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 that represents a clinically significant change in ACT has been demonstrated to be 3 units (Schatz et al 2009).

2.2. [redacted]

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a 24-week treatment, multicenter, open-label, randomized, parallel group comparison feasibility study of SoC treatment versus using the 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 24-week, open-label treatment period with Visit 2 (either in-person or remote) at Week 12 and Visit 3 at Week 24, 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 4:3 ratio, respectively, to 1 of 2 parallel groups (Table 4), stratified by investigational center.

Table 4: Description of Treatment Groups

DS group	SoC group
FS eMDPI[a] + App	Current ICS/LABA and any additional controller medication for asthma (except for biologics)
Albuterol eMDPI + App	Current rescue medication
DHP (Cloud solution)	Not applicable
Provider-facing dashboard	Not applicable

[a] iHCP can add another controller medication other than an ICS with LABA, including a biologic, to the DS patient's treatment, if needed.
Albuterol eMDPI=Albuterol electronic multidose dry powder inhaler; App=smart device application; DHP=Digital Health Platform; DS=Digital System; FS eMDPI=fluticasone propionate/salmeterol electronic multidose dry powder inhaler; ICS=inhaled corticosteroid; iHCP=investigational center health care provider; LABA=long-acting beta$_2$ agonist.

The DS group patients will use the FS eMDPI and the Albuterol eMDPI with a common App, DHP (Cloud solution), and dashboard. The SoC group patients, who will include eligible patients treated with their current treatment provided by the investigational center to the patient, based on asthma guidelines, will not use the DS during the treatment period. Similar data will be collected regarding outcomes for both groups: ACT after 24 weeks, BMQ, BIPQ, Mini-AQLQ, and WPAI questionnaire responses, and the frequency of CAEs.

All patients will have a screening/baseline visit (Visit 1), at which they will be asked if they own a smart device and use different applications on their smartphones. A baseline ACT score for all patients, and BMQ, BIPQ, Mini-AQLQ, and WPAI questionnaire responses for patients 18 years of age or older will be collected. At Visit 1, patients in the DS group will be trained on the use of the eMDPI (including instructions on how to use both the eMDPIs and the App). Upon demonstrating competency, patients in the DS group will have their maintenance ICS with LABA switched to the FS eMDPI (at a dose of fluticasone comparable to their most recent current ICS dose) and their rescue treatment switched to the Albuterol eMDPI. All other asthma maintenance medications, except for ICS with LABA, may be continued. The iHCP can add

another controller medication other than an ICS with LABA, including a biologic, to the DS patient's treatment, if needed. Patients in the SoC group will be reimbursed or given a voucher to use to purchase their existing maintenance ICS with LABA and rescue medications. Patients in the DS group will receive a new FS eMDPI device at Visit 1 and 1 FS eMDPI device and 1 Albuterol eMDPI device at Visit 2. Periodically after Visits 1 and 2, patients will be shipped a new FS eMDPI device, which they will need to pair with the App. The patient will immediately stop using the old device and switch to the new device. Extra Albuterol eMDPI devices may be shipped as needed, based on the clinical judgment of the investigator. Upon receipt, the patient will pair the new device with the App and will immediately stop using the old device and switch to the new device. To trigger direct-to-patient (DTP) shipments, after Visit 1, the investigational center will receive periodic email reminders to access the interactive response technology (IRT) system to confirm the dose of test IMP to be shipped to the patient. Confirmation of the dose is required before the next shipment can be sent.

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

The SoC group will be followed according to the clinical judgment of the investigator; the asthma of patients in the SoC 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 SoC group, the DS group patients will be followed by the investigational centers with the addition of objective information on FS eMDPI and 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, along with any other additional information about the patient, as per their clinical judgement, to modify patients' asthma management. The investigator may, if indicated, modify the patient's regime, including adding asthma controllers or biologics as otherwise clinically indicated in the judgement of the investigator. 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, Visit 3, and any Clinically Driven Assessments, 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.

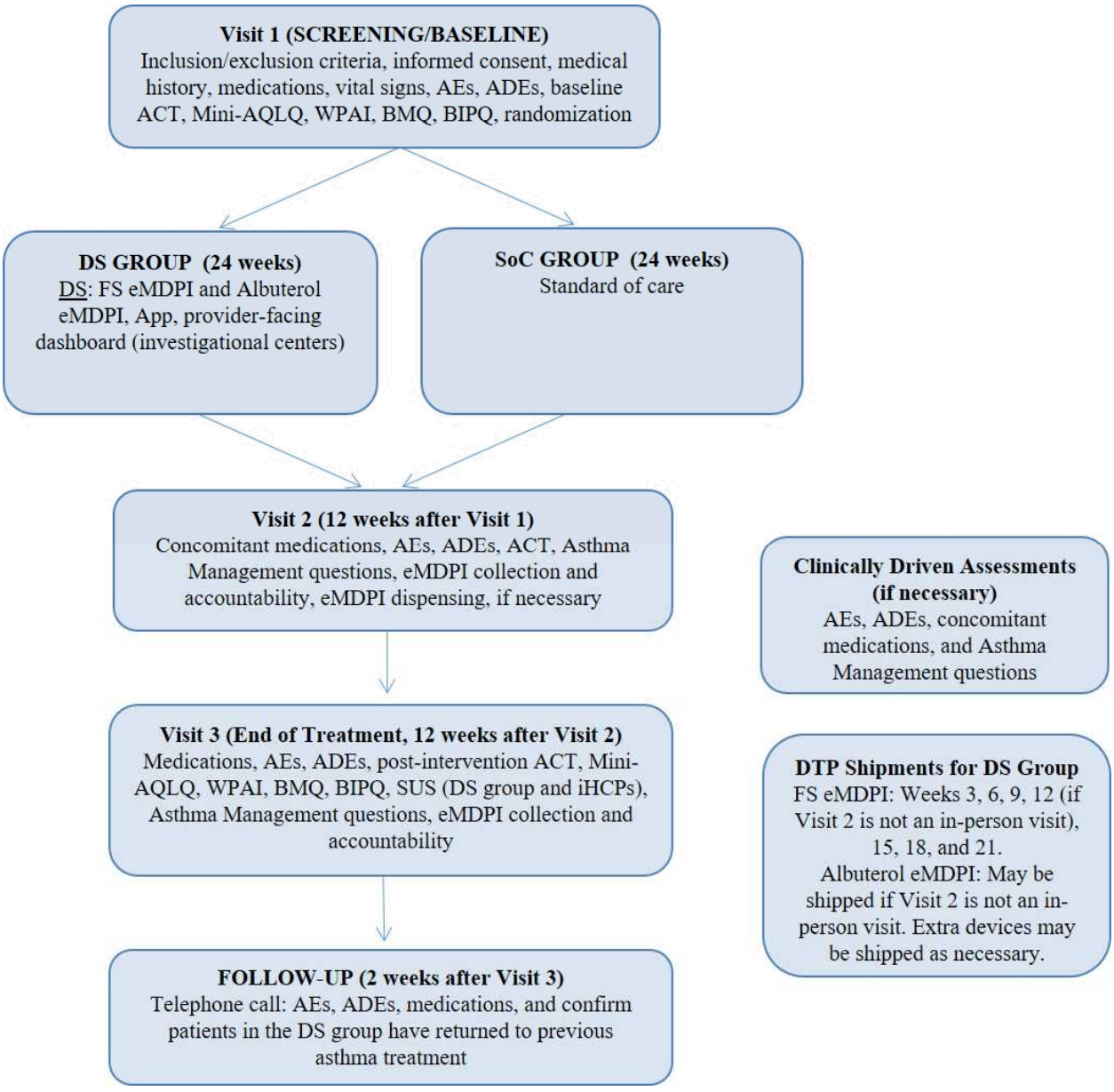
Visit 2 (if it is an in-person visit) will include dispensing of new inhalers to the DS group patients and return of used or unused inhalers that were dispensed to the patients previously. New FS eMDPI devices will continue to be shipped directly to patients periodically after Visit 2 until the end of treatment. The ACT will be completed and scores registered.

At the end of the treatment period (24 weeks), final assessments of the DS and SoC groups will be completed, as specified in Table 5, and the rest of the inhalers that were dispensed to the DS group patients will be returned. A follow-up telephone call will be made by the investigational

center to all patients, 2 weeks later, and will confirm that the DS group patients have returned to their 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; ADE=adverse device effects; AEs=adverse events; Albuterol eMDPI= albuterol sulfate electronic multidose dry powder inhaler; App=smart device application; BIPQ=Brief Illness Perception Questionnaire; BMQ=Beliefs about Medicines Questionnaire; DTP= direct-to-patient; DS=Digital System; FS eMDPI=fluticasone propionate/salmeterol electronic multidose dry powder inhaler; iHCP=investigational center health care providers; Mini-AQLQ=Mini Asthma Quality of Life Questionnaire; SoC=Standard of Care; SUS=System Usability Scale; WPAI= Work Productivity and Activity Impairment.
Note: The BIPQ, BMQ, Mini-AQLQ, WPAI, and SUS questionnaires will be completed by patients 18 years of age or older.

3.2. Planned Number of Patients and Countries

A total of 388 patients will be enrolled in the study (accounting for 10% early dropouts) and the total number of evaluable patients is planned to be 350 (200 patients in the DS group and 150 patients in the SoC 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 45 investigational centers. The study is expected to start in Q1 2021 and last until approximately Q2 2022.

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 SoC groups and the associated operational characteristics will be similar to the absolute differences and operational characteristics of the DS and SoC 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 FS eMDPI DS and 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 5. 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 5: Study Procedures and Assessments

Study period	**Screening/ Baseline visit**		**Treatment period (24 weeks)**							**Follow-up telephone call[a]**	**Clinically driven assessment(s) (if necessary)**
									End of treatment/ ET visit		
Visit number	**Visit 1**	**DTP**	**DTP**	**DTP**	**Visit 2[b]**	**DTP**	**DTP**	**DTP**	**Visit 3**		
Treatment week		**W3**	**W6**	**W9**	**W12**	**W15**	**W18**	**W21**	**W24**	**W26**	
Day and allowed time windows	**Day 1[c]**				**84 days ±3 days**				**168 days +3 days**	**182 +7 days**	
Procedures and assessments											
Informed consent/assent	X										
Inclusion and exclusion criteria	X										
Medical history	X										
Current medication and treatment history related to asthma	X										
Inform patients of study restrictions and compliance requirements	X										
ACT[d]	X				X[e]				X		
Mini-AQLQ and WPAI[d]	X								X		
BMQ-S11 and BIPQ[d]	X								X		
Assign patient number and provide unique email account for DS group patients	X										
Train DS group in use of test IMP	X										
Dispense test IMP to DS group											
FS eMDPI[f]	X	X	X	X	X	X	X	X			X
Albuterol eMDPI[g]	X				X						
Dose confirmation of test IMP in IRT[h]	X	X	X	X	X	X	X	X			X[i]
Registration and onboarding (App)	X										

Study period	**Screening/ Baseline visit**		**Treatment period (24 weeks)**							**Follow-up telephone call[a]**	**Clinically driven assessment(s) (if necessary)**
									End of treatment/ ET visit		
Visit number	**Visit 1**	**DTP**	**DTP**	**DTP**	**Visit 2[b]**	**DTP**	**DTP**	**DTP**	**Visit 3**		
Treatment week		**W3**	**W6**	**W9**	**W12**	**W15**	**W18**	**W21**	**W24**	**W26**	
Day and allowed time windows	**Day 1[c]**				**84 days ±3 days**				**168 days +3 days**	**182 +7 days**	
Procedures and assessments											
Adverse events and adverse device effects inquiry	X				X				X	X	X
iHCP will ask Asthma Management questions regarding adherence, inhaler technique, treatment adjustments, and biologic medication usage					X				X		X
Vital signs measurement	X								X		
Concomitant medication inquiry	X				X				X		X
Administer post-intervention PRO (SUS) to DS group patients[j]									X		
Administer SUS to iHCPs									X		
Test IMP collection and accountability					X				X		
Remove App from the patient's smart device (DS group)									X		
Confirmation that patient has returned to previous asthma treatment (DS group)										X	

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

[b] This visit may be in-person or remote.

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

[d] The ACT is to be completed first by all patients, followed by the Mini-AQLQ, WPAI questionnaire, BMQ, and then the BIPQ, all to be completed by patients 18 years of age or older, and should precede any discussion between the patient and investigational center personnel.

[e] If necessary, this questionnaire may be administered by telephone for this visit.

[f] At Visit 1, patients will be provided the test IMP, along with training on use and proper technique, by the investigational centers. New FS eMDPI devices will be shipped directly to the patient periodically after Visits 1 and 2. Upon receipt, the patient will pair the new device with the App. The patient will immediately stop using the old device and switch to the new device. If Visit 2 is in-person at the investigational center, a new FS eMDPI device will be dispensed at that visit.

[g] Patients will receive an Albuterol eMDPI device, along with training on use and proper technique, at Visit 1 [Day 1] and Visit 2 [Week 12]). Extra Albuterol eMDPI devices may be shipped as needed, based on the clinical judgment of the investigator. Upon receipt, the patient will pair the new device with the App. The patient will immediately stop using the old device and switch to the new device.

[h] To trigger DTP shipments, after Visit 1, the investigational center will receive periodic email reminders to access the IRT system to confirm the dose of test IMP to be shipped to the patient. Confirmation must occur within ±2 days of the email date and is required before the next shipment can be sent. The investigational center will be asked to confirm the dose of FS eMDPI and to specify whether an Albuterol eMDPI should be included in the next shipment (if not already scheduled). The 3-day visit windows do not apply to dose confirmation. Email reminders will be triggered based on the date of the previous visit or DTP shipment. If there is a need to send an additional DTP shipment outside of the regularly scheduled shipments (eg, for an additional or replacement device), it will be done in addition to the scheduled shipments.

[i] Dose confirmation at a Clinically Driven Assessment visit should be performed only if the patient's dose is being changed at this visit.

[j] 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 ET visit. Each investigational center will receive 1 SUS questionnaire, regarding the use of the dashboard, to complete following the last patient visit at the investigational center.

ACT=Asthma Control Test; App=smart device application; BIPQ=Brief Illness Perception Questionnaire; BMQ-S11=Beliefs about Medicines Questionnaire-Specific; DS=Digital System; DTP=direct-to-patient; eMDPI=multidose dry powder inhaler with integrated electronic module; ET=early termination; FS=fluticasone propionate/salmeterol; iHCP=investigational center health care provider; IMP=investigational medicinal product; IRT=interactive response technology; Mini-AQLQ=Mini Asthma Quality of Life Questionnaire; PRO=patient-reported outcome; SUS=System Usability Scale; W=week; WPAI=Work Productivity and Activity Impairment.

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 indicated below and 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 a moderate- to high-dose ICS with LABA.

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

e. The patient is willing to discontinue all other maintenance ICS with LABA medications and rescue medications and replace them with the study-provided FS eMDPI and Albuterol eMDPI, respectively, for the duration of the trial, if randomized to the DS group. All other asthma maintenance medications, except for ICS with LABA, may be continued.

f. 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. [Revision 1] 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.

b. 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.

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

d. 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.

e. The patient has a diagnosis of chronic obstructive pulmonary disease (COPD) or asthma-COPD overlap (ACO).

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

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

h. 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 judgement of the investigator as part of their asthma management and remain in the study.)

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

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 FS eMDPI or 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 SoC 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; 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 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 FS eMDPI and 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 resigned.

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 DSs consist of 4 devices each:

Test IMPs:

- FS eMDPI DS with 4 component devices:
  - Device 1: FS eMDPI
  - Device 2: Patient-facing smart device App (same for both IMPs)
  - Device 3: DHP (Cloud solution, same for both IMPs)
  - Device 4: Provider-facing dashboard (same for both IMPs)
- Albuterol eMDPI DS with 4 component devices:
  - Device 1: Albuterol eMDPI
  - Device 2: Patient-facing smart device App (same for both IMPs)
  - Device 3: DHP (Cloud solution, same for both IMPs)
  - Device 4: Provider-facing dashboard (same for both IMPs)

At Visit 1, patients in the DS group will be trained on the use of the eMDPI (including instructions on how to use both the eMDPIs and the App). Upon demonstrating competency, patients in the DS group will have their maintenance ICS with LABA switched to the FS eMDPI (at a dose of fluticasone comparable to their most recent current ICS dose) and their rescue treatment switched to the Albuterol eMDPI. All other asthma maintenance medications, except for ICS with LABA, may be continued. The iHCP can add another controller medication other than an ICS with LABA, including a biologic, to the DS patient's treatment, if needed. Patients in the SoC group will be reimbursed or given a voucher to use to purchase their existing maintenance ICS with LABA and rescue medications. Patients in the DS group will receive a new FS eMDPI device and 1 Albuterol eMDPI device at Visit 1 and 1 FS eMDPI device at Visit 2. Periodically after Visits 1 and 2, patients will be shipped a new FS eMDPI device, which they will need to pair with the App. The patient will immediately stop using the old device and switch to the new device. Extra Albuterol eMDPI devices may be shipped as needed, based on the clinical judgment of the investigator. Upon receipt, the patient will pair the new device with the App and will immediately stop using the old device and switch to the new device. To trigger DTP shipments, after Visit 1, the investigational center will receive periodic email reminders to access the IRT system to confirm the dose of test IMP to be shipped to the patient. Confirmation of the dose is required before the next shipment can be sent.

Patients will be instructed to return all inhalers to the investigational center at Visit 2 and at the end of treatment visit or Early Termination (ET) visit.

5.1.1. Test Investigational Medicinal Products

The FS eMDPI (marketed as AIRDUO DIGIHALER) is formulated in lactose and delivers drug to the airways as a fine powder without the use of propellants. The inhaler is a multidose, inhalation-driven, dry powder inhaler for oral inhalation that meters 55 mcg, 113 mcg, or 232 mcg of fluticasone propionate with 14 mcg of salmeterol from the device reservoir and delivers 49 mcg, 100 mcg, or 202 mcg of fluticasone propionate with 12.75 mcg of salmeterol, respectively, from the mouthpiece per actuation. The inhaler contains 60 actuations; the inhaler is equipped with a dose counter that shows only even numbers and counts down to "0."

The FS eMDPI has integrated electronics (eModule) that store and transmit information related to inhaler use via Bluetooth to the DIGIHALER App installed on a smart device. The eModule does not control or interfere with how patients use the inhaler to take their inhalations. The inhaler can be used with or without the App.

The system stores and transmits information about inhaler use and helps a patient use their inhaler correctly. In regular use, patients are expected to open the yellow cap, inhale through the mouthpiece, and close the cap to receive an inhalation.

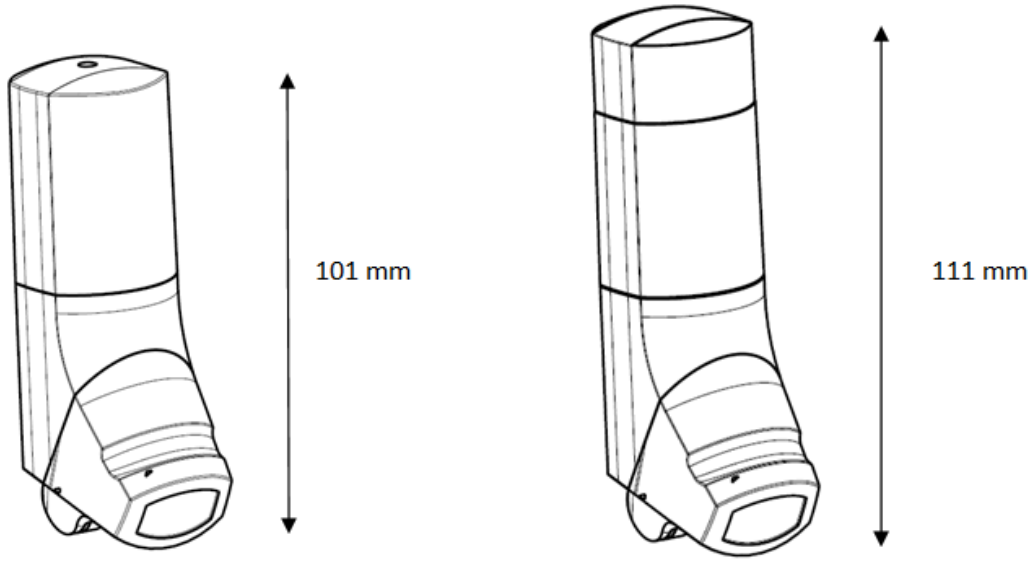
Albuterol MDPI (marketed in the US as PROAIR DIGIHALER) is an inhalation-driven eMDPI containing a blend of albuterol sulfate and alpha-lactose monohydrate. The inhaler contains 200 actuations, each delivering 90 mcg of albuterol base ex-mouthpiece; the inhaler is equipped with a dose counter that shows 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. As with the FS eMDPI, the eModule stores and transmits information related to inhaler use via Bluetooth to the DIGIHALER App installed on a smart device; the same DIGIHALER App is used for both the FS eMDPI and the Albuterol eMDPI.

The on-board electronics and power sources are fully integrated into the eMDPIs and are designed to operate for the life of the inhalers without intervention, ie, the batteries do not require replacement or recharging.

The addition of the required electronics has no impact on the pharmaceutical performance of the inhalers 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 6 and in the IBs.

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 3), investigational center personnel will remove the App from the patient's smart device.

5.1.1.1. Starting Doses and Dose Levels

The prescribed dose of FS eMDPI will be 113 mcg/14 mcg or 232 mcg/14 mcg, 1 inhalation, twice daily.

The prescribed dose of Albuterol eMDPI 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 FS eMDPI Inhalation Powder and Albuterol eMDPI Inhalation Powder combination products. The intention of the App is to engage patients with asthma 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 App compatible with iPhone operating systems (iOS) and Android operating systems that will store data locally on the patient's smart device and in the cloud (DHP) when the user is online. The App will receive a patient's inhaler use/event data automatically 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. 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 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 6: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Test IMP	Placebo IMP	Reference IMP
Trade name and INN, if applicable, or company-assigned number	FS eMDPI	Albuterol eMDPI	None	SoC asthma medications
Formulation	Inhalation powder	Inhalation powder	NA	Inhalation aerosol and/or inhalation powder
Unit dose strength(s)/Dosage level(s)	fluticasone propionate/salmeterol inhalation powder, 113 mcg/14 mcg 232 mcg/14 mcg	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	Oral inhalation	NA	Oral inhalation
Dosing instructions/Dosing schedule/Titration periods/Treatment periods	1 inhalation, twice daily	1 to 2 inhalations every 4 to 6 hours, as needed	NA	NA
Packaging	NA	NA	NA	NA
Manufacturer	Teva Pharmaceutical Industries, Ltd. Jerusalem, Israel, or Teva Pharmaceuticals Ireland, Waterford, Ireland	Teva Pharmaceutical Industries, Ltd. Jerusalem, Israel, or Teva Pharmaceuticals Ireland, Waterford, Ireland	NA	NA

Albuterol eMDPI=Albuterol sulfate electronic multidose dry powder inhaler; FS eMDPI=fluticasone propionate/salmeterol electronic multidose inhaler; IMP=investigational medicinal product; INN=International Nonproprietary Name; NA=not applicable; SoC=Standard of Care.

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 IMPs received, and any discrepancies are reported and resolved before use of the IMPs.

The IMPs 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 IMPs using a Randomization and Trial Supply Management (RTSM) system.

5.2.2. Labeling

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

5.2.3. Accountability

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

The investigator is responsible for ensuring that deliveries of IMPs for initial distribution to patients and other study materials from the sponsor are correctly received, recorded, handled, and safely and properly stored in accordance with national and local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive IMPs, and only authorized personnel at the investigational center may supply or administer IMPs. All IMPs 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 IMPs according to the instructions on the labels, if applicable; or will give instructions in an appropriate form. Patients will be instructed to return all IMPs (empty, partially used, and unused inhalers) to the investigational center at Visit 2 and the end of treatment/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. Empty, partially used, and unused inhalers will be collected at the end of the study, and all data will be downloaded from the inhalers.

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

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Doses of Test Investigational Medicinal Products

The prescribed doses of FS eMDPI used in this study (now approved by the US FDA as AIRDUO DIGIHALER) are 113 mcg/14 mcg or 232 mcg/14 mcg, 1 inhalation, twice daily.

AIRDUO DIGIHALER is indicated for the treatment of asthma in patients 12 years of age or older. AIRDUO DIGIHALER is recommended at a dosage of 1 inhalation, twice daily (55/14 mcg, 113/14 mcg, or 232/14 mcg). The 55/14 mcg dose will not be used in this study since patients with an ACT score of less than 19 will require a higher dose of ICS. To date, the overall results of clinical studies provide robust and consistent evidence that AIRDUO DIGIHALER is effective for the treatment of asthma in adult and adolescent patients.

The prescribed dose of Albuterol eMDPI (now US FDA approved as PROAIR DIGIHALER) used in this study is 90 mcg, 1 to 2 inhalations every 4 to 6 hours, as needed. 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 end of treatment/ET 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 Visit 2 and the end of treatment visit (Visit 3), patients will be asked whether they have taken any medications (other than IMPs), 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

The investigator will be responsible for dispensing IMPs, training patients on the correct use of IMPs, return of IMPs, 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. Since the Albuterol eMDPI (IMP) is a rescue medication, it will be used on an "as needed" basis.

5.8. Randomization and Blinding

This is an open-label study and patients will be randomly assigned to the DS group or SoC group in a 4:3 ratio stratified by investigational center, using a RTSM system. Further details on randomization procedures will be provided in the Statistical Analysis Plan. 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 FS eMDPI DS and 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 1st questionnaire completed by all patients during a study visit (followed by the Mini-AQLQ, WPAI questionnaire, BMQ, and then the BIPQ, respectively, all completed 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 Visit 1, Visit 2, Visit 3, or at the ET visit. For Visit 1, Visit 3, or the ET visit, the ACT will be administered in person at the investigational center. For Visit 2, the ACT may be administered by telephone. 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 (or by telephone) 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. Mini Asthma Quality of Life Questionnaire

The Mini-AQLQ is a reduced version of the Asthma Quality of Life Questionnaire (AQLQ). It was developed with patient input and is psychometrically validated (Juniper et al 1999). It accesses 15 items related to symptoms, activity limitations, emotional function, and environmental stimuli, and collects domain and total scores for analysis. The Mini-AQLQ will be answered by patients, 18 years of age or older, at the investigational center at Visit 1, Visit 3, or at the ET visit. The Mini-AQLQ should be the 2nd questionnaire completed during a study visit following the ACT.

6.1.3. Work Productivity and Activity Impairment Questionnaire

The WPAI questionnaire is used to measure work productivity and activity impairment (Reilly et al 1993). Four metrics are included: absenteeism (percentage of time missed from work due to asthma in the past 7 days), presenteeism (percentage of impairment while at work due to asthma

in the past 7 days), overall work impairment (aggregate of absenteeism and presenteeism), and activity impairment (percentage of impairment in daily activities due to asthma in the past 7 days). The WPAI questionnaire will be answered by patients, 18 years of age or older, at the investigational center at Visit 1, Visit 3, or at the ET visit. The WPAI questionnaire should be the 3rd questionnaire completed during a study visit following the Mini-AQLQ.

6.1.4. 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 3, or at the ET visit. The BMQ-S11 should be the 4th questionnaire completed during a study visit following the WPAI questionnaire.

6.1.5. Brief Illness Perception Questionnaire

The BIPQ is an 8-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. 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 patients, 18 years of age or older, at the investigational center at Visit 1, Visit 3, or at the ET visit. The BIPQ should be the 5th questionnaire completed during a study visit following the BMQ.

6.1.6. 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 3 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 the 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 forced

expiratory volume in 1 second (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 7):

Table 7: 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

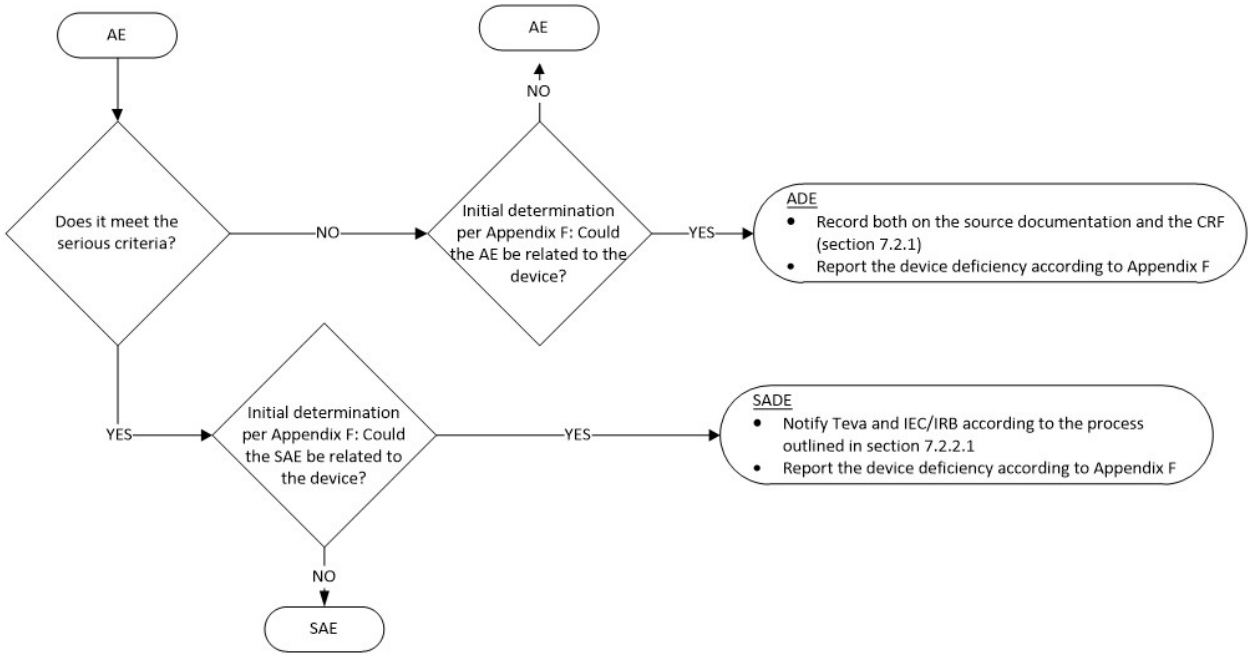
The investigator will report to the sponsor, without unjustified delay, all serious adverse device effects (within 24 hours); this information shall be promptly followed by detailed written reports as described below.

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.
6. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.

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 5.

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

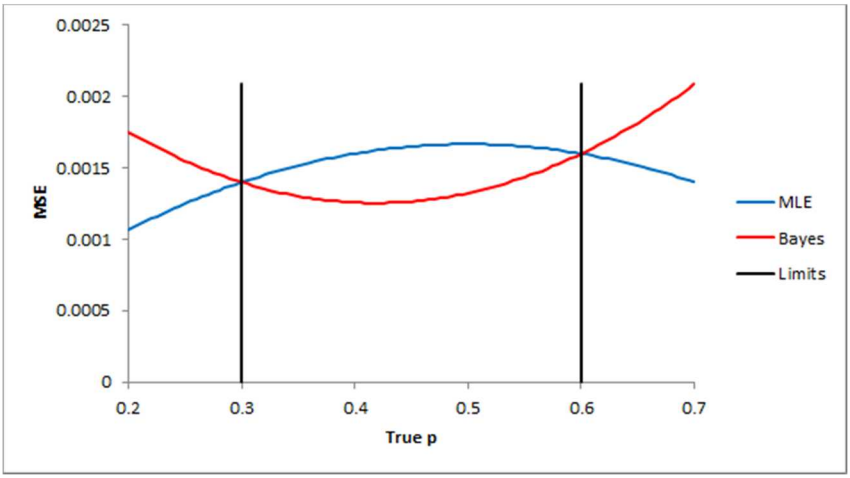
The sample size was selected based on a Bayesian approach which allows for a range of underlying proportions rather than a fixed predefined value.

A total of 388 patients will be enrolled in the study (accounting for 10% early dropouts), 200 patients in the DS group and 150 patients in the SoC group, to be available for analysis. The sample size determination was made assuming binomial distribution for the primary endpoint. An informative prior for the SoC group (Beta [9.52, 11.88]) was selected to reflect the belief that the response rate of the SoC group is between 30% and 60% (most likely 45%, Merchant 2016) and the effect size between groups of 13% difference in response rates was considered clinically meaningful.

In addition, an informative prior for the SoC group was selected to ensure that the mean square error for the Bayes estimate from the informative prior is superior to the maximum likelihood estimate over a range of 30% and 60% of anticipated proportion for SoC group.

It should be noted that both power and Type 1 error are dependent on the absolute difference between the DS and the SoC 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



MLE=maximum likelihood estimation; MSE=mean squared error

A non-informative prior (Beta [0.5,0.5]) for the DS group was selected due to lack of availability of data in the DS group.

With assumptions of response rates of 58% and 45% for the DS and SoC groups, respectively, sample size and randomization ratio, the probability of the posterior odds ratio (OR) of

improvement (ie, OR>1) for the DS group versus the SoC group of at least 0.95 is about 82%. This will ensure a 1-sided 5% Type 1 error rate and 78% power for an effect size for 13% difference between the groups provided that the proportion of responders in the SoC group is 45%.

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 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 either FS eMDPI or Albuterol eMDPI for the DS group or SoC medication for the SoC group) and at least 1 postbaseline assessment on any of the study endpoints.

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, [redacted] endpoint analyses.

9.2.3. Safety Analysis Set

The safety analysis set will include all patients in the DS group who receive at least 1 dose of IMP and all patients in the SoC 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.

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 all endpoints, 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 randomizing; 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 [n], %).

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 (n, mean, standard deviation [SD], 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 for the DS and SoC groups achieving 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 ACT units from baseline at the end of the 24-week treatment period.

9.5.2. Secondary Endpoints

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

- number of discussions 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 24-week treatment period for the DS group.

Secondary endpoint #3 is the change from baseline in adherence to maintenance treatment (FS eMDPI), defined as the proportion of actual inhalation doses taken out of the total number of inhalation doses prescribed over the 24-week treatment period.

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 SoC groups, patients 18 years of age or older, describing their behavioral profile at baseline and at the end of the study.

Secondary endpoint #5 is the change from baseline measured by the WPAI questionnaire, completed by patients 18 years of age or older in both groups, at baseline and at the end of the 24-week treatment period.

Secondary endpoint #6 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.

Secondary endpoint #7 is to evaluate the safety of FS eMDPI and Albuterol eMDPI including the following for all patients in both groups:

- adverse event data
- adverse device effect data

9.5.3. [redacted]

[redacted]

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. Population: The patients met all of the inclusion criteria and none of the exclusion criteria. The mITT analysis set will be the primary analysis set for the primary endpoint.
2. Variable: The primary endpoint will be a binary response variable at Week 24. A patient will be defined as a responder if the patient achieves an ACT score of greater than or

equal to 20 or an increase of greater than or equal to 3 ACT units from baseline to Week 24. Otherwise, the patient will be defined as a nonresponder.

3. Intercurrent events: Treatment discontinuation due to an adverse event, lack of efficacy, technology failure, disliking the DS, disliking IMP, or other reasons. For those who discontinue the treatment before Week 24, no further data will be collected.
4. Population-level summary: The primary endpoint will be analyzed using a logistic model, where binary variable responder rate (Yes/No) will be modeled through logit link function, with baseline ACT score and treatment as explanatory factors. For those who discontinue the treatment before Week 24 due to technology failure, disliking the DS, or disliking IMP, the patients will be defined as nonresponders; for those who discontinue early not due to these reasons, the response at the ET visit will be used. The mean and 95% credible intervals of the response rates and OR from the posterior distributions will be calculated and presented. An informative prior will be assumed for the model coefficient for treatment and non-informative priors will be assumed for all other model coefficients. The details for the data analysis will be specified in the Statistical Analysis Plan.

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 (n, mean, SD, 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. [redacted]

[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 5.

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 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, SD, 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, 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 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.

15. REFERENCES

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 01 Dated 19 April 2021

The primary reasons for this amendment are to update and expand the exclusion criteria to preclude patients that participated in a previous Digihaler study and to clarify the BIPQ 8-item questionnaire will be used for this study. 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. 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).

Changes to the Protocol

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)		
In addition to assessing the technical reliability experienced by patients using the DSs, the study also uses 4 patient questionnaires, the Beliefs about Medicines Questionnaire (BMQ), the Brief Illness Perception Questionnaire (BIPQ), the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ), and the Work Productivity and Activity Impairment (WPAI) Questionnaire, for ~~all~~ patients in both groups, 18 years of age or older, 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 DSs, the study also uses 4 patient questionnaires, the Beliefs about Medicines Questionnaire (BMQ), the Brief Illness Perception Questionnaire (BIPQ), the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ), and the Work Productivity and Activity Impairment (WPAI) Questionnaire, for patients in both groups, 18 years of age or older, 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.	Clarified phrasing.
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 General Study Design and Study Schematic Diagram		
All patients will have a screening/baseline visit **(Visit 1)**, at which they will be asked if they own a smart device and use different applications on their smartphones.	All patients will have a screening/baseline visit (Visit 1), at which they will be asked if they own a smart device and use different applications on their smartphones.	Revised for clarity and specificity.

Original text with changes shown	New wording	Reason/Justification for change
Section 3.2 Planned Number of Patients and Countries		
The study is planned to be conducted in the US in approximately **45**~~35~~ investigational centers. The study is expected to start in Q1 2021 and last until approximately Q2 2022.	The study is planned to be conducted in the US in approximately 45 investigational centers. The study is expected to start in Q1 2021 and last until approximately Q2 2022**.**	Updated to reflect the number of investigational centers participating in study study at the time of amendment.
Section 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 indicated below and detailed in Section 16.**	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 indicated below and detailed in Section 16.	Clarified changes to eligibilitycriteria have been implemented and provided reference to the location and rationale for these changes.
Section 4.2 Patient Exclusion Criteria		
a. [Revision 1] 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.	a. [Revision 1] 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.	Criterion revised to exclude patients with previous Dighihaler exposure.
Section 5.1 Investigational Medicinal Products Used in the Study		
Patients in the DS group will receive a new FS eMDPI device ~~at Visit 1 and 1 FS eMDPI device and 1 Albuterol eMDPI device at Visit 2.~~ **and 1 Albuterol eMDPI device at Visit 1 and 1 FS eMDPI device at Visit 2.**	Patients in the DS group will receive a new FS eMDPI device and 1 Albuterol eMDPI device at Visit 1 and 1 FS eMDPI device at Visit 2.	Correction. Patient is to receive a 1 Albuterol eMDPI device at Visit 1 along with the FS eMDPI device; Albuterol eMDPI is not dispensed at Visit 2.
Section 6.1 Assessments of Patient-Reported Outcomes		
~~All patient-reported outcomes (PROs) will be completed by patients 18 years of age or older.~~	N/A. Deletion.	Correction. The ACT is completed by all patients; the Mini-AQLQ, WPAI, BMQ, and BIPQ are completedy by patients 18 years of age and older in both groups; and the SUS is completed bypatients 18 years of age or older in the DS group.
Section 6.1.5 Brief Illness Perception Questionnaire		
"The BIPQ is a**n** ~~9~~**8**-item questionnaire designed to rapidly	"The BIPQ is an 8-item questionnaire designed to rapidly	Correction; the 8-item questionnaire will be used in this study.

Original text with changes shown	New wording	Reason/Justification for change
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.”	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. For this questionnaire, the general word 'illness' can be replaced by the name of a particular illness such as asthma.”	
Section 9.5.2 Secondary 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.
Appendix A CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS		
[redacted] ~~Teva Pharmaceuticals~~ [redacted] ~~Phone:~~ [redacted] ~~Mobile:~~ [redacted] ~~Email:~~ [redacted] [redacted] **Teva Pharmaceuticals** **Phone:** [redacted] **Email:** [redacted]	[redacted] Teva Pharmaceuticals Phone: [redacted] Email: [redacted]	Updated the contact information to the current Sponsor’s Representative of Global Patient Safety and Pharmacovigilance.
Appendix B STUDY PROCEDURES AND ASSESSMENTS BY VISIT		
Direct-to-patient (DTP) shipments of FS eMDPI will be made to patients in the DS group at Weeks 3, 6, 9, 12 (if Visit 2 is not an in-person visit),	Direct-to-patient (DTP) shipments of FS eMDPI will be made to patients in the DS group at Weeks 3, 6, 9, 12 (if Visit 2 is not an in-person visit),	Clarified DTP shipment procedures: iHCPs to confirm patients paired the inhaler with the App upon receipt.

Original text with changes shown	New wording	Reason/Justification for change
15, 18, and 21, with additional shipments as needed. **The investigational center healthcare provider (iHCPs) will check the dashboard to confirm that patients have immediately paired the new inhaler with the Digihaler App upon receipt and discontinue using the previous one.** Extra Albuterol eMDPI devices may be shipped as needed, based on the clinical judgment of the investigator. The investigational center will receive periodic email reminders to access the interactive response technology (IRT) system to confirm the dose of test **investigational medicinal product (**IMP**)** to be shipped to the patient. Confirmation of the dose must occur within ±2 days of the email date and is required before the next shipment can be sent.	15, 18, and 21, with additional shipments as needed. The investigational center healthcare provider (iHCPs) will check the dashboard to confirm that patients have immediately paired the new inhaler with the Digihaler App upon receipt and discontinue using the previous one. Extra Albuterol eMDPI devices may be shipped as needed, based on the clinical judgment of the investigator. The investigational center will receive periodic email reminders to access the interactive response technology (IRT) system to confirm the dose of test **investigational medicinal product (**IMP**)** to be shipped to the patient. Confirmation of the dose must occur within ±2 days of the email date and is required before the next shipment can be sent.	

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted]
Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study	[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]
Contract Research Organization	[redacted]

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

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

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 Mini Asthma Quality of Life Questionnaire (Mini-AQLQ) and Work Productivity and Activity Impairment (WPAI) questionnaire to patients 18 years of age or older
- administer Beliefs about Medicines Questionnaire (BMQ) and Brief Illness Perception Questionnaire (BIPQ) questionnaire 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 applications (App)
- train patients in the DS group on use and proper technique of the multidose dry powder inhaler with integrated electronic module (eMDPI)
- dispense fluticasone propionate/salmeterol electronic multidose dry powder inhaler (FS eMDPI) and albuterol electronic multidose dry powder inhaler (Albuterol eMDPI) to patients in the DS group*

  * Direct-to-patient (DTP) shipments of FS eMDPI will be made to patients in the DS group at Weeks 3, 6, 9, 12 (if Visit 2 is not an in-person visit), 15, 18, and 21, with additional shipments as needed. The investigational center healthcare provider (iHCPs) will check the dashboard to confirm that patients have immediately paired

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

the new inhaler with the Digihaler App upon receipt and discontinue using the previous one. Extra Albuterol eMDPI devices may be shipped as needed, based on the clinical judgment of the investigator. The investigational center will receive periodic email reminders to access the interactive response technology (IRT) system to confirm the dose of test investigational medicinal product (IMP) to be shipped to the patient. Confirmation of the dose must occur within ±2 days of the email date and is required before the next shipment can be sent.

- reimburse or dispense voucher to patients in the Standard of Care (SoC) group

2. **Procedures for Visit 2 (Day 84 ±3 days)**

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

- administer ACT to all patients (If necessary, the questionnaire may be administered by telephone for this visit.)
- iHCP asks Asthma Management questions
- conduct adverse events and adverse device effects inquiry
- conduct concomitant medication inquiry
- dose confirmation of test IMP in IRT
- resupply FS eMDPI and Albuterol eMDPI, if necessary (If Visit 2 is not an in-person visit, the devices may be shipped directly to the patient.)
- perform FS eMDPI and Albuterol eMDPI collection and accountability (if Visit 2 is an in-person visit)

3. **Procedures for End of Treatment/Early Termination Visit (Visit 3, Day 168 +3 days)**

The following procedures and assessments will be performed at Visit 3:

- conduct adverse events and adverse device effects inquiry
- conduct concomitant medication inquiry
- measure vital signs
- iHCP asks Asthma Management questions
- administer post-interventional ACT to all patients
- administer Mini-AQLQ, WPAI questionnaire, 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 iHCPs
- perform FS eMDPI and Albuterol eMDPI collection and accountability
- remove the App from the patient's smart device

4. **Clinically Driven Assessments (If Necessary)**

A Clinically Driven Assessment may be performed via a telephone call or an on-site visit at any time during the study at the patient's request and/or as deemed necessary by the investigator. For DS patients, the investigator will have access to information from the FS eMDPI and 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 FS eMDPI or 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 24-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
- dispense FS eMDPI or Albuterol eMDPI, as needed (if on-site and necessary). If the patient's dose is being changed at this visit, it will be necessary to access the IRT system to confirm the dose of test IMP for the next DTP shipment.
- iHCP asks Asthma Management questions

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

5. **Procedures for Follow-up Telephone Call (Day 182 + 7 days)**

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

- conduct adverse events and adverse device effects 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

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.

Important 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 an important protocol deviation. Important 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. Important protocol deviations will be identified and recorded in the patient's source documents. All important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important 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 important protocol deviation. If such patient has already completed the study or has withdrawn early, no action will be taken but the deviation 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

1. 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.

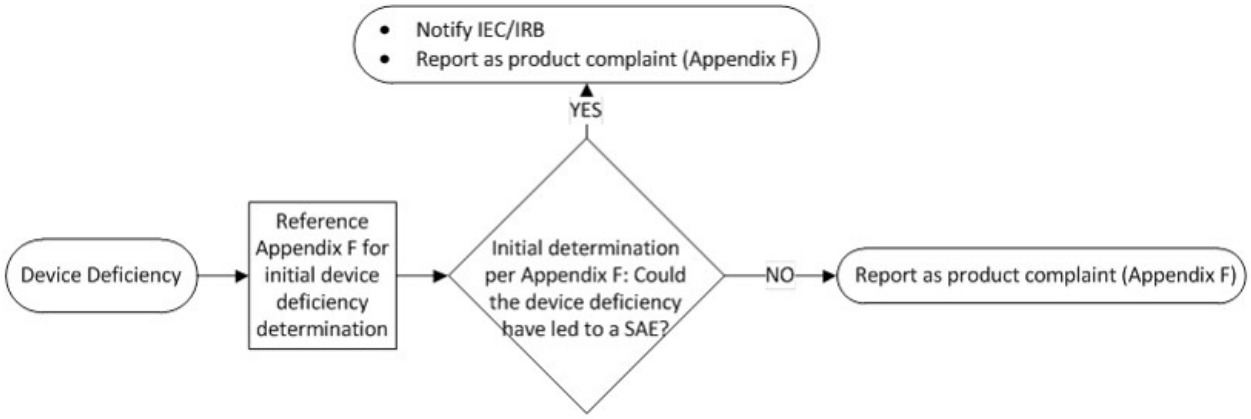
A device deficiency is defined as any inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety, or performance (Appendix Figure 1). This definition includes malfunctions, use errors, inadequate labeling (eg, unintelligible label, incorrect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

Use Step	Use Error	Potential Hazard Situation	Potential Harm
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.